THE EFFECT OF
LONG TERM TREATMENT WITH DICOUMAROL
IN
MYOCARDIAL INFARCTION

A CONTROLLED CLINICAL STUDY

BY

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GRUNE & STRATTON, INC
NEW YORK LONDON

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Made and Printed in Norway
by Oslo University Press

Ki tes B ktrykk ri O lo

TO

CARL MULLER

Preface

The investigations presented in this study were carried out in Ulleval Hospital Department VIII in the period 1950–1956 while I was employed as Assistant Physician there

I would like to express my heartfelt gratitude to the head of the Department Professor Carl Muller for his unfailing interest in my work for encouragement and valuable advice His teaching and great experience in cardiology have been a constant source of inspiration

I am greatly indebted to the former head of Department VII Professor R Hatlehol and the head of Department IX Professor H J Ustvedt for their friendliness and permission to make use of the material from their departments

I also wish to thank my former chief Professor P A Owren The basic knowledge of blood coagulation and anticoagulant therapy which I was taught as assistant and research fellow in his department and laboratory was a necessary prerequisite for this investigation

I am particularly grateful to Professor E Sverdrup for invaluable help and advice in the statistical investigation of my observations His genuine interest in my problems was a real encouragement and inspiration during the preparation of this study

I am also indebted to Dr P Amundsen in the Roentgen Department in Ulleval Hospital who kindly carried out all the radiological examinations and to the head of the Department of Pathology Dr E Hval for his permission to make use of the autopsy reports

Special thanks are due to Miss Sigrid Efjestad and Miss Inga Bjørnstad who were my assistants in the laboratory from the very beginning of the investigation for their dependable and accurate work their kindness and unfailing loyalty through many years I also want to thank their colleagues in the medical laboratories for valuable assistance and the nurses and office staff in Depts VII VIII and IX for their helpfulness during my work

I am indebted to the librarian of Ulleval Hospital Miss Ingrid Kobro and her assistants for their help in procuring the literature

To my wife I wish to express my warm gratitude for her great tolerance and for invaluable assistance in the preparation of this study

I gratefully acknowledge financial support from Johan H Andresen J L Tiedemanns Tobaksfabrik s Medisinske Fond

Finally I wish to thank Dr Susan Schanche who has translated this paper from Norwegian to English

Ulleval Hospital Dept VIII
Oslo Norway January 1957

Christopher Juel Bjerkelund

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CHAPTER I

Background to this study

In this study problems related to long term anticoagulant therapy with dicoumarol in patients after acute myocardial infarction will be discussed

The isolation (1939) and synthesis (1940) of dicoumarol 3 3 methylene bis (4 hydroxycoumarin) by *Karl Paul Link* and his co workers were soon followed by experiments on the anticoagulant properties of this substance As early as February 1941 *Bingham Meyer and Pohle* published the results of their first experiments on dogs and men and in June the same year a similar report appeared by *Butt Allen and Bollman* The prophylactic value in experimental thrombosis was investigated by *Dale and Jacques* (1942) *Richards and Cortell* (1942) *Bollmann and Preston* (1942) *Thill Stafford Spooner and Meyer* (1943) and others There were soon many reports on the clinical use of dicoumarol as an anticoagulant for prophylaxis and treatment of thromboembolic disease

Already in 1941 the effect of dicoumarol on a few cases of acute myocardial infarction had been tried It was not until 4–5 years later that the results of treatment of larger groups of patients were published *Wright* (1945 1946) *Nichol and Page* (1946) and *Peters Geyther and Brambel* (1946) almost simultaneously published their experiences of treating 76 44 and 50 cases respectively

Definite evidence of the effect of treatment was first available from the large controlled American investigation of 1031 cases started on the initiative of the American Heart Association in spring 1946 and published by *Wright Marple and Beck* (1948 1954) The results of this well planned and thorough investigation are well known Briefly it was shown that anticoagulant therapy with dicoumarol in acute myocardial infarction during the first 4 weeks produces a definite reduction of thromboembolic complications and of mortality This difference was also verified by autopsy

These results have been supported by many other publications including *Holten s* (1950 1951) large combined investigation from hospitals in Denmark and *Tulloch and Gilchrist s* (1950) thorough clinical trial from Edinburgh

A statistical comparison of the results in 20 controlled investigations which include a total of about 5 500 cases of acute myocardial infarction shows that anticoagulant therapy in the acute phase reduces both the incidence of thromboembolic complications and the mortality by about 50 % (see *Wright Marple and Beck* 1954 pages 200 and 312)

Short term anticoagulant therapy in acute myocardial infarction has often been criticised and accepted sceptically The haemorrhagic complications form the main basis for criticism This is less pertinent now that increased experience of the dosage has reduced the significance of such episodes

Apart from the question of the danger of haemorrhage objections have been made to the routine use of dicoumarol in *all* cases of acute myocardial infarction *Russek et al* (1951 1952) and *Russek and Zohman* (1952 1953 1954) have in a series of articles maintained that anticoagulant therapy is indicated and is of undoubted value in the more serious infarction cases (poor risks) But in the milder cases (good risks) the thromboembolic complications are so rare and the prognosis with conservative treatment so good that the little to be gained by anticoagulant therapy would be more than cancelled by the complications of the treatment Russek s intermediary point of view has more recently been supported by many other authors

Evans (1954) however in his attack on the treatment is much more extreme and temperamental He condemns the large publicity which the treatment has had (see also *Russel and Zohman* 1953) points out on the basis of previous autopsy studies that coronary thrombosis is only found in 43 % of the cases of acute myocardial infarction questions the statistical results and concludes That anticoagulant treatment in coronary occlusion will go the way of other discarded remedies is certain Let it go soon Let it go now before remorse weighs too heavily on those who may continue for a little time longer to advocate its use

The indications for anticoagulant therapy in acute myocardial infarction undoubtedly vary from case to case But as mentioned by Wright and others there is as yet no certain method of knowing which patients are safe and which liable to thromboembolic complications The large natural variations in the prognosis of acute myocardial infarction also make it especially difficult to assess the effect of treatment However the convincing figures from many well controlled investigations and the effect of treatment theoretically expected cannot be explained away The authors who doubt or deny the effect of treatment usually base themselves on retrospective investigations and none of them have given such a good clinical basis as some of the authors who have confirmed the effect

It is shown in the investigations mentioned that the good results of anticoagulant therapy in acute myocardial infarction depend on the fact that treatment prevents mural endocardial thrombosis subsequent emboli in the pulmonary and general circulations—and venous thrombosis One is therefore hardly justified in concluding that this form of treatment also prevents arterial thrombosis including coronary thrombosis itself which is in many respects thought to be of a different nature and related to other pathogenetic factors The evidence for such an effect has previously been very sparse and uncertain and it is this question that will form the basis of this study

CHAPTER II

The problem of the investigation. Theoretical and practical considerations for the solution of the problem

The main question posed in this investigation is the following:

Will continuous anticoagulant therapy after acute myocardial infarction improve the prognosis in a given patient in relation to a similar patient without this form of treatment? In other words will the long term result of this therapy be a reduction in mortality and in incidence of recurrent infarction and perhaps a decrease in the number of thromboembolic complications?

For those considering starting such an investigation there are many important questions to be answered. The most important of these can be grouped under the following 3 headings:

I. Is there a theoretical basis for expecting such an effect of treatment? We are in other words interested in the *pathogenesis of coronary occlusion* and especially in the aetiological role played by *thrombosis*.

II. Is it possible to solve the problem within a reasonable period of time? In other words what is the *prognosis* for patients who have survived acute myocardial infarction? Are the number of deaths and recurrent infarctions in the first months and years after a myocardial infarction sufficiently large for it to be possible to show a difference in a reasonably sized controlled clinical trial?

III. Are the necessary conditions present for the investigation to be put into practice?

The two main points here are: (1) Is it possible in a reasonable time to collect a sufficiently large number of patients for the material and can it be assumed that these patients will attend the follow up clinics regularly for observation? (2) Is a dependable and accurate method available for the control of the anticoagulant treatment as a guide for the dosage of dicoumarol?

Each of these questions will now be examined in more detail and if possible answered.

Pathogenesis of coronary occlusion

Everyone agrees that the primary disease in the majority of cases of myocardial infarction is arteriosclerosis (atherosclerosis, atheroma) of the coronary arteries which is demonstrated in 90–100 % of the cases. Little is yet known about the aetiology and pathogenesis of arteriosclerosis. All the unsolved problems in this field will not be mentioned here as they have no direct bearing on

or not arterial thrombi can also grow centrally against the blood stream and thus attack new arterial branches causing an extension of the infarction It can easily be imagined that a thrombus could form in the stationary column of blood in front of an occluding thrombosis *Zollinger and Papacharalampous* (1953) have investigated this point in cases of coronary thrombosis By making serial sections some longitudinal and some transverse through thrombosed coronary arteries they showed that appositional growth in a central direction often occurs with older occluding thrombi Also on mural non occluding thrombi they found growth of fresh thrombi not only peripherally but also centrally Similar observations have been made by others studying coronary occlusion and coronary thrombosis in serial sections The authors point out the considerable theoretical possibilities for anticoagulant therapy in such cases This conception is also supported by observations published by *Wright Marple and Beck* (1954 p 213) They found clinical signs of extension of the originally infarcted area in 40 of 442 control patients compared with 19 of 589 patients who had anticoagulant therapy

Recanalisation of thrombus

There is neither clinical nor experimental evidence to indicate that anticoagulants can cause the thrombus to dissolve or to disappear On the other hand there are investigations which indicate that anticoagulant therapy favours the natural tendency to recanalisation of occluding thrombi In experiments on the ear vein in rabbits *Wright Kubik and Hayden* (1952) showed that with tromexan recanalisation occurred after an average of about 3 weeks In control animals it was at least 8 weeks or nearly 3 times as long before recanalisation could be shown *Wright and Kubik* (1953) also produced thrombosis in the femoral arteries of rabbits In the animals who got tromexan recanalisation occurred after an average of 3½ weeks and the process started already after 24 hours The femoral arteries in untreated animals were still occluded after several months

The role of intimal bleeding in the pathogenesis of coronary occlusion

The question of the role of intimal bleeding in the pathogenesis of coronary occlusion has had renewed interest in connection with anticoagulant therapy

Paterson (1936 1938 1939) found that vascularisation of the intima of coronary arteries by capillaries direct from the lumen never occurs in normal arteries but is a usual finding in atherosclerosis It is especially prominent if occluding thrombosis is present He found proliferating capillaries in the intima in 15 out of 16 such cases and it was most pronounced if there was advanced organisation of the occluding thrombus He often showed bleeding in atheromatous plaques both with and without thrombosis in the lumen of the artery He relates this bleeding to the capillaries which are especially dispo ed to rupture partly because of the high intra capillary pressure and the large fluctuations in pressure as a result of the origin of the capillaries direct from the arterial lumen and partly because of the

poor support the capillaries have in the loose atheromatous tissue surrounding them. The author found intimal bleeding in 32 out of 37 consecutive cases of recent coronary thrombosis and he maintains that there must be a pathogenetic connection between intimal bleeding and thrombosis.

Paterson's opinion that bleeding in the intima plays a large part in the pathogenesis of coronary occlusion is supported by the observations of many other workers. *Wartmann* (1938) reports 7 cases of fatal coronary occlusion of which 6 were caused directly by extensive sub-endothelial haemorrhage in the intima and haematoma formation with subsequent occlusion. In 1 case the bleeding broke through to the lumen with secondary thrombotic occlusion. He also studied serial sections from 41 occluded coronary arteries and found that occlusion was caused by an intra-mural haematoma alone in 6 cases and by a combination of intra-mural haematoma and thrombosis in 14 others.

On the basis of thorough studies of the blood vessel supply to the arterial wall *Winternitz, Thomas and LeCompte* (1938) also consider that intimal bleeding is an important factor in the pathogenesis of thrombosis. They maintain, however, like many other authors that the histological findings are often difficult to interpret. When a vessel is finally completely filled with granulation tissue the events leading to the occlusion cannot be reconstructed with any degree of certainty.

Horn and Finkelstein (1940) and *Nelson* (1941) also agree with Paterson and Wartmann that in many cases intimal bleeding can be the immediate cause of coronary thrombosis.

English and Willius (1943) found bleeding in the intima in 40 % of 135 cases who died of coronary disease. In all the cases where thrombosis was shown in the artery they also found bleeding in the intima. However they do not believe that these haemorrhages are the most important factor in the development of thrombosis and coronary occlusion.

Figures from other investigations give intimal bleeding a much less prominent place. *Wright Smith* (1936) found intimal bleeding as the cause of coronary occlusion in only 1 of his 495 cases and *French and Dock* (1944) in 5 out of 80 cases (6 %). *Yater et al* found fresh haemorrhage in 26 (5.8 %) and old haemorrhage in 29 (6.4 %) of 450 consecutive fatal cases of coronary disease. A slightly higher incidence was found by *Papacharalampous and Zollinger* (1953), i.e. 35 (27.8 %) of 126 cases. Of these however 21 had simultaneous thrombosis. *Wright, Marple and Beck* (1954) demonstrated intimal bleeding in only 3 of 89 cases (3.4 %) and in 2 of these thrombosis was the immediate cause of the occlusion. Of 24 cases of recurrent infarction during the observation period no intimal bleeding was shown either in anticoagulant treated or untreated patients.

It has often been suggested that intimal bleeding in coronary occlusion is a contra-indication to anticoagulant therapy. However, as far as is known, there are no investigations which indicate or prove that this form of treatment provokes an increased number of occlusions of haemorrhagic pathogenesis.

Other pathogenetic factors in coronary occlusion

The most important pathogenetic factors in coronary occlusion have been mentioned above. But there are other factors that are sometimes of decisive importance.

Muller (1938, 1939) has pointed out that angina pectoris, coronary disease and sudden cardiac death often in relatively young patients are common in patients with *xanthomatous deposits*. He stresses that the disease is familial, inherited as a dominant factor, either as clinically demonstrable xanthomatosis or as hypercholesterolaemia. The arteries and especially the coronary arteries are the site of predilection for xanthomatous deposits. This familial xanthomatosis—Muller's disease—which seems to be relatively seldom mentioned, is probably a more frequent cause of coronary occlusion and myocardial infarction—especially in the young than the impression usually given in the literature. Thus *Waaler* (1956) found such cases in 6–7 % of 275 cases of angina pectoris. How often the xanthomatous plaques themselves in the coronary arteries are the cause of pronounced narrowing, perhaps complete occlusion, and how often there is a secondary thrombosis is as yet unknown.

Different types of *arteritis* in the coronary arteries are also of primary significance for occlusion in some cases. The best known example of this is the narrowing of the coronary opening and first 10–12 mm of the coronary arteries not infrequently seen in syphilitic mesaortitis. Periarteritis nodosa and other types of arteritis can also rarely be the cause of coronary occlusion either alone or as the starting point for thrombotic occlusion. *Papacharalampous and Zollinger* (1953) found arteritic changes in 11 (8.7 %) of their 126 cases, but in 7 of these thrombosis was a contributory cause of the occlusion.

Rarely coronary occlusion is caused by an *embolus*, a phenomenon seen especially in bacterial endocarditis.

Finally, it has been maintained that myocardial infarction may occasionally develop without demonstrable narrowing of the coronary arteries. *Gross and Sternberg* (1939) have described 15 cases where they only found moderate atherosclerotic changes in the coronary arteries but no narrowing or occlusion. A number of factors affecting the myocardial nutrition, including fall in the aortic blood pressure, relative ischaemia due to cardiac hypertrophy, anaemia and reflex vasoconstriction or spasm of the coronary arteries are discussed by these authors. A striking fact not mentioned by them is that in 14 of the 15 cases the myocardial infarcts were not fresh but old and fibrotic. It is therefore possible that there was narrowing or occlusion when the infarction occurred and that the subsequent regressive changes obliterated the most important traces of this.

Is thrombosis a pathogenetic factor in the development of atherosclerosis?

Over a hundred years ago *Rokitansky* (1852) stated that atheroma was the result of excessive deposition of blood derivatives, especially fibrin, on the inner surface of the arteries. This point of view was strongly questioned by *Virchow*

(1856) who maintained that atheroma was an inflammatory process and the thickening of the wall was the product of reactive proliferation of the connective tissue cells in the intima

The more recent general opinion is that atherosclerosis begins as a degenerative change with deposition of fat in the deep layers of the intima followed by fibrous tissue proliferation

Duguid (1946) has given new life to Rokitansky s old thrombosis theory He has shown that fibrous thickening of the intima with narrowing of the lumen can be the result of a gradual organisation of the occluding thrombi in the coronary arteries According to Duguid s investigation such thrombi by organisation with ingrowth of connective tissue cells and capillaries shrinking recanalisation and covering with endothelial cells can give an anatomical picture indistinguishable from atherosclerosis A similar organ ation also occurs in mural thrombi The author points out that white thrombi which contain fibrin are usually completely permeated by connective tissue On the other hand red thrombi which contain a large number of tightly packed blood cells besides fibrin are often only covered on the surface by connective tissue especially if they are relatively large Central softening and fatty degeneration occur and result in an anatomical picture confusingly like atheromatous plaques

More recently in many new investigations and with new histological material *Duguid* (1948 1949 1952 1954 and 1955) *Rannie and Duguid* (1954) and *Duguid and Robertson* (1955) have confirmed this opinion

On the basis of these investigations Duguid has come to the conclusion that there are two pathogenetically different types of atherosclerosis—cholesterol lesions and thrombogenic lesions When the lesions are well advanced it is often difficult to decide which pathogenetic factor was originally responsible He maintains however that the cholesterol lesions which lead to weakening and gradual softening of the different layers of the arterial wall usually result in *dilatation* of the lumen Thrombosis on the other hand which occurs on the inner wall of the artery and does not harm the original layers of the wall leads to *narrowing* of the arterial lumen Duguid maintains that since it is this narrowing which is dangerous thrombosis is the pathogenetic factor of most significance in fatal coronary disease

More recently many other workers have supported Duguid s opinion *Harrison* (1948) and *Heard* (1952) produced experimental pulmonary arteriosclerosis in rabbits by injection of finely divided clots into the ear vein They caused a fibro elastic thickening of the intima indistinguishable from spontaneous arterio sclerosis *McLetchie* (1952) produced similar intimal changes in the pulmonary arteries by injecting a mixture of Russell viper venom and rabbit brain thrombo plastin *Heard* (1949) has also confirmed Duguid s findings of microscopic fibrin deposits on the intima in the aorta and has shown the same changes in the first

part of the renal arteries which are especially liable to atherosclerosis. Similar experiments have also been carried out by *Crauford and Levene* (1952) with the same result.

Geiringer (1951) examined 300 aortas and 100 coronary arteries for vascularisation of the intima. He shows that the normal intima is not vascularised but nourished from the lumen (see p. 18, Paterson). If the intima increases in thickness beyond a certain limit, the nourishment and oxygen supply will be insufficient. The result is an ingrowth of capillaries into the intima either from the arterial lumen or through the media from the blood vessel network in the adventitia, or simultaneously in both these ways. Geiringer is in complete agreement with Duguid's thrombosis theory, which he believes sheds a new light on these problems. The transmedial vascularisation from the adventitia occurs with the slow gradual growth of the intima beyond the critical thickness. Vascularisation from the lumen on the other hand is a sign of a sudden catastrophic increase in the thickness of the intima due to thrombosis. Demonstration of such vascularisation can therefore, according to Geiringer, be taken as a definite sign of intimal changes of thrombogenic origin. The capillary blood supply to the intima is easily damaged, resulting in infarction necrosis and scar formation of the intima. Such an area can be the site for secondary thrombotic deposition.

The investigations referred to here suggest that thrombosis is not, as generally thought, only a secondary terminal process in atherosclerosis, but in many cases possibly a significant pathogenetic factor for its development. This point of view has not yet been generally accepted. However, it may prove to be a fruitful working hypothesis for further investigations in this important field of medicine. *McLetchie* gives an impression of this in his discussion: "while much remains to be done, a purely thrombogenic basis of atheroma must receive serious consideration. It is certain that if this is correct, it opens up completely new fields for prophylactic anticoagulant therapy in arterial disease."

Prognosis after survival from acute myocardial infarction

The second question asked was the following: Is it possible *within a reasonable period* to decide whether or not long term anticoagulant therapy after myocardial infarction has prophylactic value?

There are many publications dealing with the immediate prognosis in acute myocardial infarction, i. e. the prognosis in the first weeks after the infarct. What we are interested in, however, is the outlook for patients who have survived the first month.

More recently quite a few investigations have been published dealing with the long term prognosis. For an investigation to be able to answer our question, the following conditions must be fulfilled:

(1) All the patients in the investigation must have come under observation *at the latest* 1 month after the attack. Patients who come under observation (e g by admission to hospital) at a later stage have already survived for part of the period in which we are interested. If such patients are counted as observed from the end of the first month an error will be introduced as the patients would not have been in the investigation if they had died between the end of the first month and the day of admission. Consequently a too good prognosis will be found. The same is naturally true whether the observation starts from the beginning of the acute attack or 2 or 3 months afterwards.

(2) The diagnosis must have been able to have been made from information available at the end of the first month. If patients were included in whom the diagnosis was made retrospectively, e g at post mortem, a bias would arise in the opposite direction to the possible bias mentioned under point 1. Thus a too poor prognosis will be the result.

Disregard of these principles is certainly the main reason for the unreasonably large variations found for the immediate mortality in the literature. The principles certainly play a lesser part in the assessment of the prognosis beginning at the end of the first month or later. However this is difficult to judge as very few workers state the interval between the beginning of the attack and the beginning of the observation period.

In addition to these difficulties often being ignored in the available investigations into the prognosis, the analysis of the data is often incomplete or directly misleading. In many investigations no notice is taken of the fact that the observation period for those who have survived is sometimes very short, so that many patients would probably die before, for example, 3 years had elapsed since the infarct. The influence of age on the prognosis is often not considered. This is often because most investigations are too small to be divided up into homogenous groups without a danger of chance variation influencing the results.

On account of these facts more detailed mention of the following papers will not be made: *White* (1926), *Parkinson and Bedford* (1928), *Conner and Holt* (1930), *Cooksey* (1935), *Willius* (1936), *Levine and Rosenbaum* (1941), *Rathe* (1942), *Boas* (1951) and *Gertler et al* (1951).

A brief discussion will now be made of some other publications which do give some basis for answering our question. Among these a number of papers published in the course of the present investigation have also been included. The investigations referred to here are in the author's opinion sufficient to demonstrate what is known today about the life expectancy in patients who have survived an acute myocardial infarct. The most important data from these investigations are collected in *Table 2*. In a few cases the figures were recalculated by the author so that they could be expressed uniformly for a comparison to be made.

It is clear that the different authors have found considerable differences in the prognosis. The number of survivors after 3 years thus varies from 87 % (*Morris*

TABLE 2

Prognosis after survival from acute myocardial infarction

Author (s)	Average age	No of cases who survived an acute myocardial infarct and were alive after: 4 weeks	2 months	3 mth	The percentage of these cases alive the following number of years after the acute attack: 1	3	4	5	10
Palmer (1937)*	58			212	97	84		74	38
Bland and White (1941)	56	162			81	60		50	31
Katz et al (1949)	58		353		76	47		22	
Eckerstrom (1951)	66 7	109			67	41		30	
Sigler (1951)*	55 8	1176						45	11
Waldron and Constable (1951)*	51 6			1551	91			69	55
Morris et al (1952)*	40 64	119			97	87		82	
Smith (1953)	55 5	85			88	71		64	53
Robb and Marks (1953)* +	51 5			166	93	81	74	70	51
Cole et al (1954)*	56 7		285					67	44
Westlund and Hougen (1956)	63 1	929			80	60	55		

* The patients included in these investigation had only had one myocardial infarct at the beginning of the period of observation

\+ In this investigation the length of the survival time was not reckoned from the beginning of the acute attack but from when the patients were admitted to disability (Probably 3 months after the beginning of the attack)

et al) to 41 % *(Eckerstrom)* and the number of survivors after 5 years varies from 82 % *(Morris et al)* to 22 % *(Katz et al)* The large differences are certainly partly due to the very different age compositions of the different materials Thus *Waldron and Constable s* investigation only included patients under 60 years while the patients were all under 65 in *Morris et al s* and *Robb and Mark s* investigations both of which showed a good prognosis On the other hand *Eckerstrom s* investigation included a large proportion of very old patients The average age in his investigation was 66 7 years or about 10 years older than most of the other investigations (excluding the 3 with especially young patients mentioned above) Another factor which probably contributed to the large differences in mortality was that some of the investigations (as shown in the table) only included patients with their *first* attack while others included patients who had had acute myocardial infarction whether it was the first or a subsequent attack This last group included *Katz et al* and *Eckerstrom s* investi

gations both of which had a bad prognosis The variation noted from [illegible] to 3 months between the start of the attack and the beginning of the observation time naturally also played a considerable part

Finally the large differences certainly also depend on the many sources of error and uncertain factors which can influence this type of follow up investigation as previously mentioned Thus many authors state that their information about many of the patients was incomplete or that the follow up was impossible

A very thorough investigation into the long term prognosis in myocardial infarction has recently been published by *Westlund and Hougen* (1956) based on 1613 patients from 5 medical departments in Oslo This material has been examined statistically with respect to age and sex A large number of different subgroups have also been analysed The authors state the mortality ratio (ratio between actual and expected number of deaths) depends to a large extent on age at discharge and number of years after discharge For instance among males in the entire material the mortality ratio in the first year after discharge varied from 15 5 at ages 40–49 to 4 8 at ages 80–89 Among males 60–69 the mortality ratio varies from 8 1 in the first year after discharge to 2 1 ten years and over Rough figures making it possible to compare the duration of survival in this investigation as a whole with the other investigations were not given The figures used in Table 2 were kindly given to the author personally

In spite of the large variations the papers referred to give a definite impression that the mortality in the first years in patients who have survived an acute myocardial infarct is so large that if a form of treatment has any effect its result should easily be noticeable On this basis it should be possible to judge the value of prophylactic anticoagulant therapy within a reasonable period The large differences in the prognosis from one investigation to the next shows that any attempt to judge the effect of treatment by comparing the prognosis with previous investigations will be of little value

Cause of death in coronary disease

A high mortality in itself is not enough on which to base an investigation into the effect of anticoagulant therapy The question is also what is the cause of death in these patients? Clinical experience has taught us that in patients who have had a myocardial infarct the cause of death is usually heart disease The mode of death can however vary—new infarcts sudden cardiac death or heart failure These facts should perhaps be illustrated by some figures Of 45 cases who had survived an acute myocardial infarct by more than 4 weeks *Hochrein and Schneyer* (1936) found that in 29 % the cause of death was a new infarct 9 % died suddenly 9 % had pulmonary embolism 46 % had heart failure and in only 7 % was the cause not cardiac *Levine and Rosenbaum* (1941) report on the mode of death in 80 cases who had survived their first acute infarct Of these the cause of death in 40 % was a new infarct 35 % died suddenly 20 % had heart failure

and in only 5 % was the cause not cardiac Of 52 cases who died more than 2 months after the acute infarct *Katz Mills and Cisneros* (1949) found that in 65 % the cause of death was a new *infarct and in 20 % heart failure Sigler* (1951) found of 393 deaths from coronary disease that in 68 % the cause of death was coronary occlusion 16 % died suddenly and 15 % had heart failure *Cole Singian and Katz* (1954) give the cause of death in 171 cases who had survived their first infarct by more than 2 months Of these in 55 % it was a new infarct and 17 % had heart failure Only 10 % of the deaths had no relation to the cardio vascular system

The largest *number of recurrent infarcts after an acute infarct seem to occur* in the first years See e g *Conner and Holt* (1930) *Palmer* (1937) and *Cole Singian and Katz* (1954)

Practical conditions for the investigation

Possibilities for collecting material

The third question asked concerned the practical conditions necessary before the investigation could be started First of all would it be possible to collect a sufficiently large number of patients within a reasonable period? Could it be assumed that these patients would attend the follow up clinics regularly for observation?

In order to answer these important questions a simple numerical assessment must be made of the possibilities available

The present investigation was planned and carried out while the author was working at Ullevål Hospital Department VIII Ullevål Hospital is Oslo City's large municipal hospital and in 1950 it had 1 920 beds The hospital has three equally sized medical departments with a total of about 450 beds i e about 40 % of the medical beds available to the 440 000 *inhabitants of Oslo*

The patients admitted to these departments nearly all live in Oslo They can therefore if desirable or necessary attend follow up clinics in the departments and be seen by the specialists working there Exceptions to this usually only include patients who live out of town or abroad who are admitted if they need immediate hospital care suddenly while visiting Oslo Numerically such patients are very few

This investigation only included patients who had survived their acute infarct by at least 1 month This point will be returned to later

The investigation was further limited so that it only included patients who on admission with their acute infarct were not yet 76 years old

In the 3 departments mentioned there were *in 1949 a total of 116 patients* (78 men and 38 women) who fulfilled these conditions Therefore from these 3 departments one could expect that in about 2 years 200 patients could be collected who would be able to attend regularly at follow up clinics and perhaps

for treatment This was considered to be a satisfactory basis for starting the investigation More details about the collection of the material will be discussed in Chapter IV

Basis for control of treatment with dicoumarol

The next consideration to be taken before the investigation could be started was the control of the dicoumarol treatment itself Unless the control is well planned and dependable and accurate in practice the basis for assessment of the effect of treatment will be shaky

The development of anticoagulant therapy in Norway and especially the extensive use of long term out patient treatment in this country and in other Scandinavian countries is due largely to *P A Owren s* fundamental work Owren s first contributions to this field were based on his basic investigations into the mechanism of coagulation This is not the place to give a detailed account of these investigations Some of the main points must however be mentioned as they provide the theoretical background necessary to understand the method used in this study to estimate the effect of dicoumarol on the coagulability of the blood (Owren s PP method)

Owren s work on the mechanism of coagulation began in April 1943 with the investigation of a 29 year old woman who since she was 3½ years old had had a serious haemorrhagic diathesis She had a considerably prolonged coagulation time and the cause of her bleeding was therefore a serious failure in the mechanism of coagulation Although the prothrombin time estimated by Quick s method was also considerably prolonged Owren soon noticed that this was not due to lack of prothrombin However it took 1½ years of intense and detailed experiment before it was shown that it was due to the lack of a new previously unknown coagulation factor and this factor was isolated from the previously known coagulation factors The new factor was first called the fifth factor (*Owren* 1944 1947) and later got the name *proaccelerin*

During these investigations Owren found that different prothrombin preparations were converted to thrombin at different rates This difference was not due to proaccelerin and indicated the existence of another previously unknown conversion factor in the prothrombin preparations used This factor was temporarily called co factor V (*Owren* 1947) and is now called *proconvertin* (*Owren* 1950) It was separated from prothrombin in 1949 (*Owren and Bjerkelund*) but the final proof of its existence came when patients were found who had a haemorrhagic diathesis because this factor was lacking (*Alexander et al* 1951 *Aas* 1952 *Owren* 1952) Especial interest was focussed on proconvertin in anticoagulant therapy when it was shown that dicoumarol phenylindanedione and other oral anticoagulants caused a fall in the concentration in the plasma not only of prothrombin but to at least as great an extent of proconvertin (*Owren* 1950)

The discovery of proaccelerin made it clear that Quick s method of prothrom

bin estimation was not specific but that the prothrombin time estimated in this way was also dependent on the concentration of proaccelerin *Owren* (1947 pp 265–271) therefore developed a new one stage method of prothrombin estimation By adding Seits filtered prothrombin free ox plasma to the coagulation mixture he made certain of a constant excess of proaccelerin and at the same time a constant additional supply of fibrinogen Prothrombin time estimated with this method is thus independent of the proaccelerin concentration in the plasma under investigation and the addition of fibrinogen makes it possible to dilute the plasma and still have enough fibrinogen for clot formation A further modification of the method was described by *Owren* in 1949

Since as mentioned above proconvertin is also necessary for the conversion of prothrombin to thrombin it became clear that Owren s method was not a specific prothrombin estimation either It was shown that the Seits filtration of the ox plasma used in Owren s method not only removed prothrombin but proconvertin as well The method thus estimates the combined activity of prothrombin and proconvertin It was therefore called the PP method (prothrombin and proconvertin method) (*Owren and Aas* 1951) As dicoumarol (and other anticoagulants) cause a fall in the proconvertin concentration which is at least as great as the fall in prothrombin concentration it is clear that a method which estimates the combined activity of these two coagulation factors is theoretically very useful as a guide for dose regulation of dicoumarol

For the details of the method the reader is referred to the papers mentioned above but the advantages of the method over the usual one stage methods like for example Quick s method will be mentioned briefly

(1) Dilution (1 10) of the plasma under investigation increases the sensitivity and accuracy of the method as it allows the most favourable part of the correlation curve to be used where a difference in percentage concentration gives the greatest possible difference in the coagulation times recorded This sensitivity applies to all prothrombin concentrations even those over 100 % It is therefore possible to follow the initial fall in PP concentration which gives the first impression of the patient s sensitivity (As is well known Quick s method is not very sensitive in the range 100–50 % prothrombin) The dilution also minimises the effect of the different inhibitors and possible variation in the fibrinogen concentration in the plasma under investigation Errors which can arise because variations in the haematocrit value of the blood give a difference in the oxalate (or citrate) concentration in the plasma and inadequate recalcification will also be eliminated by dilution and by the constant relatively large addition of oxalate (or citrate) in the ox plasma The presence of small amounts of heparin in the plasma under investigation is also of no significance and the method can therefore also be used during combined administration of heparin and dicoumarol often used for the first days after an acute thromboembolic episode

(2) The method is independent of the concentration of [illegible] sample under investigation as a high constant amount of proa[illegible] by the addition of the Seits filtered ox plasma reagent The lability of [illegible] on standing has therefore no effect in contrast to in Quick s method

(3) On the other hand if the estimation is not carried out at [illegible] vertin is activated by contact with glass and the PP time is shortened (Eg[illegible] *las and Owren* 1954) In order to prevent this Owren now adds a small [illegible] of heparin 100 / per ml in 3 13 % potassium citrate Mercaptol 1 1/[illegible] added to prevent damage to the sample by bacterial contamination [illegible] technique a correct result can be obtained even if the sample under inv[illegible] is 3–4 days old This can be very important in long term out patient t[illegible] when patients are not able to attend the clinics personally and when the [illegible] must therefore be sent by post

A more detailed account of the reagents used in the PP method and the [illegible] tical technique will be given later (see pp 49–52) A more detailed accou[illegible] also be given of the methods used for administration and supervision [illegible] dicoumarol therapy The author s personal experience in this field is mentio[illegible] the foreword to this paper

On this background it was natural to take up the problem of long term p[illegible] phylactic therapy in myocardial infarction when satisfactory material could be obtained

Summary and conclusion

In this chapter the problem of the investigation is presented first This is followed by an account of the theoretical and practical considerations for the solution of the problem

On the basis of the literature the factors in the pathogenesis of coronary occlusion thought to be of greatest interest for the prophylactic value of long term anticoagulant therapy in myocardial infarction have then been discussed Although not completely exhaustive the reported data seem to be sufficient to draw the following conclusions

(1) The pathogenesis of coronary occlusion is closely related to the aetiology and pathogenesis of atherosclerosis which is to a large extent a still unsolved problem

(2) There are diverging opinions on which process preceeds the morphological changes found in coronary occlusion In advanced relatively old changes most authors agree that no one can be certain of the nature and order of the processes leading to these changes

(3) Thrombosis (in atherosclerotic coronary arteries) seems in previously published investigations to have been the immediate cause of the occlusion in about half the cases Further appositional growth of fresh thrombi in a central direction on old occluding thrombi plays a part in extension of the infarcted area

(4) Bleeding in the intima can occasionally in itself be the direct cause of occlusion In other cases such bleeding may be a contributory cause of thrombosis There is as yet no evidence that anticoagulant therapy provokes an increased number of occlusions of haemorrhagic pathogenesi

(5) There is experimental evidence showing that anticoagulant therapy favours the tendency of the thrombus to recanalisation

(6) Recent observations suggest that thrombosis may be a significant factor in the pathogenesis of atherosclerosis

It therefore seems reasonable to believe that long term anticoagulant treatment after myocardial infarction may have prophylactic value (1) By preventing new cases of coronary occlusion caused by thrombosis (2) By preventing appositional growth of fresh on old thrombi and thus hindering the subsequent extension of the infarcted area (3) By favouring recanalisation of the thrombus and (4) by thus providing better possibilities for the development of collateral vessels

On the other hand intimal bleeding represents an uncertain factor in the treatment about which little is definite at the present

It seems however theoretically possible that treatment can delay or prevent the progression of the atherosclerotic process itself

The next section deals on the basis of the literature with the late prognosis after an acute myocardial infarct and the commonest causes of death in these patients It is pointed out that most recurrent infarcts seem to occur in the first years after the original infarct It is shown that both the mortality and the incidence of recurrent infarction in the period after an infarct seem to be so high that a controlled clinical trial of reasonable size should be able to demonstrate the effect of long term anticoagulant therapy within a reasonable period

Taken on the whole it is theoretically impossible to make any calculation or definite statement at all on the prophylactic value of long term treatment after myocardial infarction or in coronary disease in general The only way to evaluate the treatment is to start a controlled clinical trial the results of which can be assessed statistically There is thus good reason to suppose that the investigation planned will serve a useful purpose and be of value for the solution of our problem The answers to the many questions on the mechanism of coronary occlusion may then come in second place

In the last section of this chapter it is shown that there were good opportunities for collecting a sufficiently large number of patients who would be able to be under continued supervision Further an account is given of the theoretical background for Owren s PP method for estimation of prothrombin and proconvertin which in this study is the basis for control of the antithrombotic effect during treatment Thus the practical conditions were present for starting the investigation

CHAPTER III

Previous publications on long term anticoagulant therapy

It has been shown in the previous chapter that both from the theoretical and practical points of view there seems to be a good basis for taking up the problem previously outlined However the following question must be answered first *has this problem already been sufficiently investigated?* If so a new investigation would be superfluous It is therefore necessary to look at the previous work in this field

As emphasised by *Owren* (1955) anticoagulant therapy is by nature prophylactic and not curative It is obviously much better to prevent a myocardial infarct or pulmonary or cerebral embolus or occlusion of an artery or vein than to treat a patient with one of these conditions In patients with often recurring thromboembolic episodes it was therefore appropriate to try long lasting perhaps permanent anticoagulant treatment for prophylaxis

Surprisingly enough neurologists began first They started a trial of continuous treatment with dicoumarol of cases of disseminated sclerosis as early as May 1942 (*Putman 1943 Putman Chiavacci Hoff and Weitzen* 1947)

As far as can be seen from the literature it was *Nichol* who introduced long term therapy into cardiology He began the treatment in February 1944 in a patient who had then had 3 serious myocardial infarcts in 13 months (*Nichol and Fassett* 1947)

At about the same time *Peters Geyther and Brambel* (1946) started using this form of treatment in a few cases of coronary thrombosis in the hope of preventing recurrences

In the autumn of 1946 *Wright and Foley* (1947) started continuous treatment with dicoumarol in patients with rheumatic heart disease atrial fibrillation and a tendency to recurring embolism

Since then many papers on long term treatment with anticoagulants of different thromboembolic diseases have appeared gradually Many of these publications are from medical centres in which the leaders and their different co workers have published their experiences at intervals dealing with an increasing number of patients who as time has passed have had increasingly long periods of treatment Further there are a few more scattered publications dealing with different aspects of long term treatment In order to avoid repetition the publications will not be discussed chronologically but first some of the scattered investiga

(4) Bleeding in the intima can occasionally in itself be the direct cause of occlusion In other cases such bleeding may be a contributory cause of thrombosis There is as yet no evidence that anticoagulant therapy provokes an increased number of occlusions of haemorrhagic pathogenesis

(5) There is experimental evidence showing that anticoagulant therapy favours the tendency of the thrombus to recanalisation

(6) Recent observations suggest that thrombosis may be a significant factor in the pathogenesis of atherosclerosis

It therefore seems reasonable to believe that long term anticoagulant treatment after myocardial infarction may have prophylactic value (1) By preventing new cases of coronary occlusion caused by thrombosis (2) By preventing appositional growth of fresh on old thrombi and thus hindering the subsequent extension of the infarcted area (3) By favouring recanalisation of the thrombus and (4) by thus providing better possibilities for the development of collateral vessels

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The next section deals on the basis of the literature with the late prognosis after an acute myocardial infarct and the commonest causes of death in these patients It is pointed out that most recurrent infarcts seem to occur in the first years after the original infarct It is shown that both the mortality and the incidence of recurrent infarction in the period after an infarct seem to be so high that a controlled clinical trial of reasonable size should be able to demonstrate the effect of long term anticoagulant therapy within a reasonable period

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Beaumont Coblentz Maurice Chevalier and Lenegre (1952) have tried treatment with dicoumarin ethyl ester sometimes combined with initial use of heparin in 40 cases of severe angina pectoris The treatment lasted for periods from 10 days to more than 6 months The authors state that the attacks of angina pectoris completely vanished in 14 cases and that the symptoms improved in a further 16 cases

Beaumont Scebat and Lenegre (1954) report their results with long term therapy of 61 cases of coronary disease with infarction or threatening infarction 14 cases of rheumatic valvular disease with multiple thromboembolic complications and 10 cases of migrating phlebitis with pulmonary embolism The duration of treatment in most cases varied from 6 months to 4 years but was 5 and 11 years respectively in 2 cases The authors consider that the incidence of thromboembolic complications during treatment was considerably less than one would expect without treatment

Burt (1954) makes out a case for cyclic dosage She gives the anticoagulant for example for 3 days and misses every 4th day so that the prothrombin value has an opportunity to rise again She has treated 74 patients with extensive arterial thrombosis or recurrent venous thrombosis and 2 patients with atrial fibrillation and a tendency to embolism Her method of dosage as one would expect leads to large swings in the prothrombin values

Reports of long term anticoagulant treatment of individual cases have been published by e g *Swedberg* (1953) on a case of migrating thrombophlebitis *Rice Ackerman and Satchel* (1950) on a case of recurrent myocardial infarction with pulmonary embolism and by *London* (1950) who describes severe haemorrhages with a fatal outcome during adequate treatment of a 70 year old woman with hypertension and generalised arteriosclerosis and warns against long term treatment in such cases

As mentioned a great many publications on long term treatment have been published from medical centres where such treatment is used regularly Most of these are by *I S Wright* and his co workers (See *Wright and Foley* 1947 *Wright* 1949 *Foley and Wright* 1949 *Wright Bourgain Foley Devitt Gross Burke Simon Lieberman Symons and Huebner* 1954 *Tulloch and Wright* 1954 *Foley Devitt Symons and Wright* 1954 etc) A great many different questions experiences and results of treatment of an increasing number of patients are discussed in these publications Here only a few of the most recent papers will be referred to briefly

In a round table conference reported in the fourth of the papers given above amongst other things the indications for long term treatment were discussed According to *Wright* this treatment is indicated in (1) rheumatic heart disease with atrial fibrillation and multiple emboli (2) recurring thrombophlebitis (3) multiple arterial occlusions if caused by thrombosis or embolism (4) recurrent myocardial infarction especially if there are thromboembolic complications

(5) idiopathic or familial tendency to thrombosis (6) recurring tendency to thrombosis and (7) less well defined in frequent attacks of angina pectoris which may indicate impending infarction and in recurring signs of cerebral vessel spasm or small thromboses According to *Wright* the treatment is more or less contraindicated in (1) marked hypertension (blood pressure over 200/110) (2) if the patient is mentally incompetent (3) if the doctor is not especially trained in the treatment or will not take on the responsibility for the relatively exacting control

Tulloch and Wright (1954) report on 227 patients treated with tromexan or dicoumarol for periods varying between 4 weeks and 8 years i e an average of about 290 days per patient The dosage was controlled using Quick s method at intervals of 2–3 days increasing to 7 days and in some cases to 10–14 days but seldom longer

The most frequent indication for treatment was thrombophlebitis (117 cases) Next came rheumatic heart disease with a tendency to peripheral or pulmonary embolism (38 cases) and myocardial infarction (32 cases) Finally there were small groups of patients with various other conditions connected with thrombosis or embolism Only intelligent and co operative patients were chosen for treatment Twenty six patients had a total of 40 certain or possible thromboembolic complications during treatment About half of these occurred when the prothrombin time should theoretically have been adequately prolonged and 3 occurred when it was excessively prolonged Treatment thus did not give complete protection

A report on some of the same patients namely 85 who had had continuous treatment for over a year (an average of 3½ years per patient) has been published by *Foley Devitt Symons and Wright* (1954) Of these 29 had rheumatic heart disease 24 had thrombophlebitis 23 myocardial infarction and 9 had various other diseases with a tendency to thrombosis and embolism The authors compare the incidence of thromboembolic episodes during the total period of observation for each of the groups of patients mentioned *before* and *after* treatment was instituted They conclude that the treatment resulted in a marked reduction of thromboembolic episodes in patients with rheumatic heart disease or recurring thrombophlebitis Previous studies of the prognosis for cases of myocardial infarction show that these patients sometimes live for many years without specific treatment They consider that long term therapy is indicated in coronary disease (1) after recurrent infarction (2) when periods of heart failure are a prominent feature and (3) when multiple embolic episodes have occurred

In Norway long term anticoagulant therapy was introduced by *Owren* in 1948 In 1952 *Owren* (1953) reported on his experiences with a group of 79 patients More recently (1954 1955) he has published the results of treatment of 247 patients who had been treated for periods varying between 1½ and 6 years The patients included

(a) 106 patients who had survived a single myocardial infarct by at least 8 weeks and had been having continuous treatment for an average of 2 6 years

per patient In this group there were 9 deaths from myocardial infarct or cases of sudden death i e a mortality of about 4 % per year There were also 3 deaths from chronic heart failure The mortality is according to Owren only about half the mortality reported in the literature in patients without anticoagulant treatment

(b) 128 patients with angina pectoris without a previous infarct were treated for an average of 2 5 years per patient There were 12 deaths from myocardial infarction or cases of sudden death and 1 death from chronic heart failure There were also 3 non fatal infarcts The mortality is thus about 5 % per year or about half that published for angina pectoris patients by *Block Crumpacker Dry and Gage* (1952)

(c) 13 patients with mitral valvular disease atrial fibrillation and a tendency to embolism These patients had a total of 25 embolic episodes during about 13 years before the treatment was started and only 1 episode (cerebral embolism) in 24½ years of treatment

Owren stresses the prophylactic value of anticoagulant therapy and concludes that it can be continued for years with a minimum of serious complications provided there is a dependable method for control of the treatment and there is close cooperation between laboratory doctor and patient

Waaler (1956) has carried out a searching detailed and thorough investigation of 275 of Owren s cases of angina pectoris The period of treatment for these patients was a total of 670 years or an average of 2 5 years per patient On comparing with *Block Crumpacker Dry and Gage s investigation* (1952) he found that the mortality was considerably lower and that this difference was statistically significant He also found that the incidence of recurrent infarction after treatment was started was significantly less than in the period before treatment Waaler had no control group for comparison and is very careful in his conclusions He found however that a large number of the patients improved so much from their angina pectoris that the cause must have been more than merely a placebo effect He does not feel justified in saying anything certain about to what extent this improvement was due to the anticoagulant therapy itself or to the accompanying regime of treatment The results were best in the group in which treatment with dicoumarol had been least intensive and stable However this group included a relatively large number of patients in whom treatment was started especially early It follows from Waaler s investigation that it is the patients with a short history who benefit most from treatment

Muri (1956) also reports good results of long term treatment with dicoumarol in 67 patients who were treated for an average of 1¾ years after an acute infarct

That opinion on anticoagulant therapy especially the indications and significance of long term therapy is also divided in the Northern countries is shown by an inquiry by Nordisk Medicin in November 1955 with contributions by *Holten Owren Broch Tybjærg Hansen Dedichen Hilden Lund and Sommerfeldt*

Nichol (see p 31) has often published his most recent experiences of an increasing number of patients with coronary disease *Nichol and Borg* (1950) published their results of treatment for periods from 3 to 62 months of 78 patients after acute myocardial infarction According to *Nichol Phillips and Jenkins* (1954) anticoagulants are useful in the following phases of coronary disease (1) impending myocardial infarction and acute coronary insufficiency (2) acute transmural infarction and (3) after these conditions have occurred given as long term treatment to prevent recurrences The authors gave prophylactic long term treatment to 295 patients for periods from 3 months to over 7 years Forty one patients (13 8 %) died while being treated 125 stopped treatment for different reasons after 1–82 months and 129 patients continued to get treatment The authors mention that the patients were chosen carefully and were told all about the object and risk of the treatment The authors are not able to say anything definite about the effect of the treatment but their experiences are sufficiently satisfactory to justify the treatment being continued

In order to illustrate the effect of long term prophylactic treatment in coronary sclerosis and myocardial infarction 10 American cardiologists have combined the results of treatment from their private practices *Nichol Keyes Borg Coogan Boehrer Mullins Scott Page Griffith and Massie* (1954 1955) The investigation included 1091 cases of which 735 had had one previous myocardial infarct 260 had multiple previous infarcts and 96 had had impending infarction without definite myocardial damage Of the patients 448 had been treated for less than 1 year 247 for 1–2 years and the rest for longer periods up to 8 years One hundred and thirty one patients died after being treated for 3 to 91 months giving a total mortality of 12 % The mortality was lowest in the group that had not had a previous infarct and twice as high in the group that had had multiple infarcts as in the group that had only had one infarct before treatment started The causes of death were as follows recurrent infarct 46 cases sudden death 31 embolism 5 heart failure 23 cerebral haemorrhage 6 non cardiac 15 and unknown 5 Three hundred and nineteen cases broke off anticoagulant treatment after 3–80 months Of these 20 died of a heart attack within a month and a further 70 died within 4 years of stopping treatment giving a mortality of 28 2 % in this group Five of the ten contributors provided a control group consisting of 417 cases that had been under observation for 3–96 months Of these there were 256 men 49 women and 112 sex not given The age distribution was not given There were 156 deaths in this group giving a mortality of 37 4 % The highest mortality among these patients was (surprisingly enough) in those who had not had a previous infarct and the mortality was the same in those who had had one infarct as in those with multiple infarcts before the observation started

The authors conclude that their data indicate that long term anticoagulant therapy reduces the mortality in patients who have had one or more attacks of myocardial infarction to less than half

Keyes Drake James and Smith (1953) have also attempted to assess the effect of long term treatment with dicoumarol after myocardial infarction with the help of an untreated control group Their treated group consisted of 63 cases of whom 31 had only had one infarct and 32 had had several All the patients were treated for 1 year and 41 of them for 2 years Treatment was only instituted in intelligent and dependable patients The control group consisted of 147 patients of whom 106 had had one infarct and 41 had had several All these patients were followed up for at least 2 years Most of the cases in this group were diagnosed before long term treatment was introduced The sex and age distributions in the two groups to be compared are not mentioned and no attempt is made to show that the two groups were comparable The authors merely state we believe variation in the extent of infarctions is similar in both groups A statistical comparison is made of the mortality in the treated and control groups in patients with one and several infarcts in the first year second year and both years to gether The authors maintain that the difference is significant for human data in all groups except the group with several infarcts during the second year of observation (the level of significance varied between 10 and 30 %) They state that about 4 times as many patients died in the group without long term treat ment as in the treated group

The controlled investigation published from Johannesburg by *Suzman Ruskin and Goldberg* (1955) seems to be more carefully carried out Their material consisted of 208 patients with myocardial infarction who had all had anti coagulant therapy during the acute phase and who had all survived the first 3 months or longer The observation time varied from 3 to 76 months The patients were not allotted to the treated and control groups according to principles decided on beforehand After surviving the acute phase the patients were asked personally and their private doctors consulted whether or not they should continue long term treatment The long term group originally consisted of 120 patients but 38 of them were excluded from the comparison because they broke off treatment The remaining 82 formed the basis of the true investigation The short term group consisted of 89 cases who had short term treatment during the acute phase for a maximum of 3 months and sometimes additional courses of short term treatment if they had recurrent infarcts The authors com pare the composition of the two groups as regards age sex incidence of previous angina pectoris previous infarction and the incidence of mild and severe cases of the first recorded infarct without finding any statistically significant difference In the long term group the mortality was 7.3 % and among the 82 patients there were 7 cases of recurrent infarction of which 3 were fatal In the short term group the mortality was 33 % and there were 24 cases of recurrent infarction of which 19 were fatal On comparing the cases with *severe* acute attacks taken alone the authors found that the mortality in the long term group was 9 % and there were 7 cases of recurrent infarction among 67 patients while the mortality in the

short term group was 46 7 % with 21 recurrent infarcts among 60 patients Heart failure during the observation period had about the same incidence in both groups but the mortality associated with heart failure was 11 8 % in the long term group and 57 1 % in the short term group

The authors conclude that patients who have had a single mild attack of myocardial infarction and who have received short term treatment seem to have a good prognosis without long term therapy The patients who seem to benefit most from long term therapy are those who not only have a severe presenting attack but have also a history of previous myocardial infarction

Haemorrhagic complications

As it is the haemorrhagic complications that have formed the most important basis for scepticism and criticism of both short and long term anticoagulant therapy a few remarks seem justified

It is obvious that if the object of a form of therapy is to reduce the coagulability of the blood there *must* be danger of bleeding It is also a fact that haemorrhagic complications have been observed in all large investigations on patients treated with anticoagulants In unexperienced hands and with unsatisfactory control severe haemorrhagic complications have sometimes been an important problem in the treatment This is especially seen in some reports written soon after dicoumarol was introduced into clinical medicine

Concerning haemorrhagic complications during short term treatment the reader is referred to the following articles *Barker Cromer Hurn and Waugh* (1945) *Allen Hines Kvale and Barker* (1947) *Duff and Shull* (1949) *Nichol* (1950) *J A M A* (editorial) (1950) *Wright and Rothman* (1951) and *Russek and Zohman* (1953)

Details on the occurrence and significance of haemorrhagic complications in *long term* anticoagulant therapy are given in the articles mentioned so far in this chapter The incidence of such complications in the different investigations can not be compared directly as it is not given in a uniform manner Some authors include with the total number of haemorrhages a large number of cases that were obviously completely insignificant clinically Others state that a given proportion of the haemorrhages observed were so mild that they were of no importance Finally some mention in passing that mild insignificant haemorrhages occurred but do not mention in what proportion of the cases

It is obvious that the number of haemorrhagic complications will increase with the length of the treatment Therefore the incidence of such complications given as a percentage of patients treated is no indication of the actual frequency of such complications *Owren* (1955) therefore now gives the incidence of haemorrhages in relation to the sum of the periods of treatment as one thus gets an impression of how *often* such complications occur If expressed in this way the incidences of haemorrhages in different investigations would be much more easily

compared Owren points out that the incidence of haemorrhages [illegible] markedly with improved technique of control and increasing experience

Looking through the literature on long term anticoagulant therapy [illegible] not get the impression either that haemorrhagic complications have [illegible] serious problem This is especially true of most large investigations pu[illegible] the last 2–3 years with a period of treatment for some patients of 2 [illegible] and more It must be said however that these investigations must be [illegible] to have been carried out by experts

By combining *Nichol and co workers* large investigation with those of [illegible] *al* (1954) *Tulloch and Wright* (1954) and *Owren* (1955) we get a total of [illegible] patients who have had long term anticoagulant therapy for a total of about [illegible] years Of these patients 8 died of haemorrhage of whom 6 had cerebral [illegible] rhage and 2 had sub endocardial bleeding into the heart muscle Considering [illegible] a large number of the patients in these investigations were elderly with [illegible] sclerosis and sometimes hypertension the number of fatal haemorrhages is [illegible] small

The fact that haemorrhagic complications do occur in all the investigations published serves as a warning that the treatment must be controlled caref[illegible] and thoroughly *Allen s* (1948) opinion certainly still holds good The [illegible] method of preventing hemorrhage is to use dicumarol expertly Even [illegible] hemorrhage will occur

Table 3 gives a general view of the most important articles previously publ[illegible] on long term anticoagulant treatment The author(s) number of cases treat[illegible] type of disease and duration of treatment are shown Further the number of patients who had clinically significant haemorrhage and the number of deaths as a result of haemorrhage are indicated

TABLE 3

Long term treatment with anticoagulants

Author(s)	No of cases treated	Diagnosis	Treatment time per case (months)	No of cases with haemorrhage	Death from haemorrhage
Peters et al (1946)	?	Myocardial infarction	–24	?	0
Allen et al (1947)	[illegible]8	Occlusive arterial disease	2–10	?	0
Nichol and Fassett (194)	5	Myocardial infarction	6–3?	0	0
Putnam et al (194)	43	Disseminated sclerosis	6–47	?	0
Wright and Foley (1947)	11	Atrial fibrillation	7 (av)	0	0
Sprague and Jacobson (1948)	1	Atrial fibrillation	15	0	0
Foley and Wright (1949)	19	Atrial fibrillation Thrombophlebitis Myocardial infarction	5–20	0	0
Hines and Barker (1949)	1	Atrial fibrillation	?4	0	0
Olwin (1949)	1[illegible]	Thrombophlebitis Myocardial infarction Disseminated sclerosis	4–?3	?	0

Author(s)	No cases treated	Diagnosis	Treatment time per case (months)	No cases with haemorrhage	Deaths from haemorrhage
Wright (1949)	22	Atrial fibrillation	[illegible]– 19	0	0
Askey and Cherry (1950)	20	Atrial fibrillation	2– 28	[illegible]	0
Cosgriff (1950)	17	Atrial fibrillation	3– 2[illegible]	3	0
London (1950)	1	Cerebral thrombosis Hypertension	8	1	1
Nichol and Borg (1950)	78	Myocardial infarction	3– 6[illegible]	28	2
Rice et al (1950)	1	Myocardial infarction	51	1	0
Beaumont et al (1952)	40	Angina pectoris	[illegible]– 6	[illegible]	0
Facquet et al (1952)	3	Atrial fibrillation	12– 30	0	0
Hellem (1952)	47	Coronary disease Thrombophlebitis Atrial fibrillation	1– 11	9	0
Cosgriff (1953)	28	Atrial fibrillation	1 – 56	6	0
Dedichen (1953)	55	Coronary disease Occlusive arterial disease	6–	4	1
Keyes et al (1953)	200	Myocardial infarction etc	6–24 approx	31	0
Lund (1953)	19	Myocardial infarction Thrombophlebitis	2 16	3	0
Owren (1953)	79	Myocardial infarction Angina pectoris Atrial fibrillation	12– 36	6	0
Swedberg (1953)	1	Migrating thrombophlebitis	34	1	0
Bay et al (1954)	115	Various thromboembolic diseases	13 (a)	6	0
Beaumont et al (1954)	85	Coronary disease Atrial fibrillation Migrating thrombophlebitis	6–132	12	0
Burt (1954)	76	Venous thrombosis Arterial thrombosis Atrial fibrillation	3– 54	10	0
Dedichen (1954)	9[illegible]	Coronary disease Occlusive arterial disease	6– 48	[illegible]	1
Foley et al (1954)	85	Atrial fibrillation Thrombophlebitis Myocardial infarction	12– 96	31	1
Nichol et al (1954)	295	Myocardial infarction	3– 84	73	1 + 1 ?
Nichol et al (1954)	1091	Myocardial infarction	3–100	220	6
Owren (1954)	247	Myocardial infarction Angina pectoris Atrial fibrillation	6– 60	19	1
Stephens (1954)	53	Various thromboembolic diseases	10 (av)	[illegible]	1
Tulloch and Wright (1954)	277	Various thromboembolic diseases	1– 96	43	1
Owren (1955)	247	Myocardial infarction Angina pectoris Atrial fibrillation	18– 72	2[illegible]	1
S zman et al (1955)	8[illegible]	Myocardial infarction	3— 76	12	2
Muri (1956)	67	Myocardial infarction	[illegible]– 40	4	0
Waaler (1956) (Owren's patients)	275	Angina pectoris Myocardial infarction	6– 60	51	3

* This figure indicates number of haemorrhagic episodes

Summary and conclusion

In this chapter an account has been given of the most important previo[us] publications on long term anticoagulant therapy It is evident that this form of treatment in the last 10–12 years has been tried in many different diseases mo[st] of which have a tendency to thrombosis and/or embolism

However the number of publications on the treatment of large groups of patients must be said to be very small and in many cases the period of treat ment is relatively short The larger investigations published are from a ve[ry] few medical centres and outside these centres the treatment seems to have bee[n] relatively little used

It is reasonable to believe that the limited use the treatment has so far had is partly because of anxiety about the complications partly because of insufficient evidence of the effect of the treatment and partly because of difficulties in proving the effect statistically Finally in clinical medicine it is new and unusual to start long term possibly life long *prophylactic* treatment with its far reaching conse quences These are probably the most important reasons for the treatment often being met with scepticism and uncertainty

On reading the previous publications it is obvious that most of them have not aimed at assessing the effect of the treatment but have simply tried to show that the treatment is practicable for ambulant patients without too great a risk It must also be said that in 1950 when this study was planned there were no other investigations which set out to prove whether or not long term anticoagulant therapy had a definite prophylactic effect

During the last 6 years some authors have published large investigations that have made it *probable* that the treatment is of value This has been done partly by comparing the incidence of thromboembolic episodes per unit of time in treated patients with the incidence in the same patients before treatment was started and partly by comparing the mortality in treated patients with the mortality from the same disease in a previous period without treatment or with the data on the prognosis in previous publications by others There are also 3 investigations in which the effect of long term treatment in coronary disease especially myocardial infarction is shown by comparison of a treated with an untreated control group It is clear that two of these investigations (*Keyes et al* 1953 and *Nichol et al* 1955) do not attempt to present a true controlled clinical trial The control group is obviously collected in retrospect and no attempt is made to show that the treated and untreated groups are comparable even as regards such simple and fundamental characteristics as age and sex distribution Also the further statistical calculations seem unsatisfactory and the results are therefore of little value as concrete evidence The third controlled investigation (*Suzman et al* 1955) seems to have been more carefully carried out and is on the whole of considerable interest However the assignment of the patients to the

treated and control groups was not carried out after pre arranged selection principles and may have been influenced by many different factors some subjective It is also not clear what the influence on the treated group has been of the fact that ⅓ of the 120 patients stopped treatment and were therefore excluded from the comparison Further another weak point must be mentioned the patients receiving long term therapy attended the clinic at regular intervals and were under close medical supervision by the authors These patients therefore had the benefit of advice about their mode of living and of the early institution of appropriate treatment when signs or impending complications developed The patients in the control group on the other hand did not get regular supervision and cardiological treatment in the clinic in the same way Thus considerable differences in the treatment of the patients in the two groups existed also apart from the long term anticoagulant therapy — Finally an account of the intensity of the anticoagulant treatment as judged by the prothrombin level is not given

It seems thus to be clear that even today 6 years after the present investigation was started there are no convincing statistical results available from carefully planned and controlled therapeutic trials of the effect of long term anticoagulant therapy after acute myocardial infarction This is striking as such investigations were suggested by *Wright and Foley* as early as 1947 and by *Nichol and Borg* in 1950 *Garb* (1955) stresses that there are many unsolved questions and doubts about the effect of dicoumarol (and other oral anticoagulants) even when used as short term treatment in acute myocardial infarction He stresses the need for more controlled investigations in this field This need is undoubtedly even greater as regards long term therapy

The most recent large investigations of patients treated for many years have shown that in experienced hands anticoagulant therapy can be given to ambulant patients without any very great risk of haemorrhage At any rate the risk is not so great that it provides a reason for rejecting the treatment Nor can the treatment as previously emphasised by *Ouren* (1955) be rejected because some investigators have not found it satisfactory and have found too many haemorrhagic and/or thromboembolic complications because of lack of experience unreliable laboratory techniques or both

On the other hand it also seems clear that if we are to continue to use a form of treatment that represents considerable inconvenience to the patients and a lot of work for the laboratories and doctors and that therefore has considerable economical consequences the value of the treatment must be proved more convincingly than has previously been the case In this way it may also be possible to make the indications for treatment more obvious This can only be done by arranging the best possible controlled clinical trial in which the course of the disease can be compared statistically in treated and untreated patients from the same period and the same source This has been the object and is the justification of this study

CHAPTER IV

Planning the investigation

As mentioned in Chapter II the object of this investigation is to assess the prophylactic value of continuous treatment with dicoumarol of patients after acute myocardial infarction It must be stressed that the effect of anticoagulants in the acute phase of the disease has no bearing on this problem In 1950 when this investigation was planned this question had already been the basis of thorough investigations which seemed to establish the value of such treatment (see pp 13–14)

This investigation was therefore planned as an observation of patients who had survived their acute infarct by at least 1 month It was further agreed that all the patients should have anticoagulants during the first month after admission Thus none of the patients were deprived of a form of treatment the effect of which seemed to be established already It was also obvious that all the patients should have as uniform treatment as possible in the interval between the acute attack and the beginning of the observation period If no anticoagulants had been given for instance to all the patients in the control group a bias might have developed probably in favour of the control group as the treated group would thus include a larger number of serious cases who had survived their acute infarct thanks to anticoagulants

Allotting patients to the treated and control groups

Choice of statistical method of selection

The first requirement when the effect of a form of treatment in a controlled clinical trial is to be assessed is that the groups to be compared are uniform before treatment (observation) begins

A large number of variables can influence the late prognosis after acute myocardial infarction These include age sex past history especially as regards previous infarction heart failure hypertension enlarged heart—and finally the severity of the infarct recorded with its effect on the function of the heart to mention some of the most important It is therefore essential that these factors affecting the prognosis should be as evenly distributed as possible between the two groups to be compared so that the groups are comparable from a prognostic point of view at the beginning of the investigation

Different methods of allotting patients to treated and control groups come to mind when one is planning a therapeutic trial and a few of them will now be discussed

It might be thought advantageous to grade (stratify) the patients into prognostic groups (strata) before allotting them to treated and control groups In other words on the basis of a great many variables some of which are mentioned above an assessment and grading of the prognosis according to fixed criteria would have to be made in each individual case All the patients in the same prognostic stratum would then for example by drawing lots be distributed between the treated and control groups

Such a method of approach would entail a great deal of extra work and considerably complicate the subsequent statistical analysis In addition the prognosis after myocardial infarction is very difficult to predict Assessment is moreover complicated by errors of a subjective psychological nature A very important practical difficulty is also that the patients to be stratified according to prognosis are not all present at the beginning of the investigation but they come up one by one in the course of several years Finally the method cannot be used without another important difficulty cropping up that will be mentioned below On the whole this method of approach seems ill suited to this investigation and offers no advantages

A chance distribution of the patients to the treated and control groups without previous stratification can be carried out in different ways for example the patients can be allotted to the two groups alternately in the order they are admitted to hospital Or they could be allotted according to whether they were admitted on even or odd dates or on the basis of the date of birth being even or odd The latter method would probably be the safest (see for example the skew distribution in *Wright Marple and Beck's* large investigation in which the method of even and odd dates of admission was used)

The use of one of the methods mentioned here also entails certain practical difficulties The main reason for rejecting such a method of approach in this investigation was however different Right from the beginning it was obvious that one of the greatest difficulties in the investigation which would last for several years would be to keep the control group intact In other words to keep the patients in this group free from long term anticoagulant therapy

Any new treatment is in the eyes of the public always the best and there was reason to fear that as the patients in the control group gradually got to know that some patients were treated in this way they would want the same themselves The significance of this in relation to allotting the patients will be mentioned In the medical departments in this hospital the patients are not in single but in larger rooms with 2 to 7 beds and in each department there is a large ward for 22 patients It is therefore unavoidable that two patients admitted for acute myocardial infarction are often in the same room During a month's

stay in hospital there would be ample opportunity for discussing and getting to know about their disease It would then be very difficult to explain to two such patients that although they had the same treatment in hospital their treatments would differ after discharge For this reason which in the author s opinion is very real and important allotting the patients by even and odd dates of birth was rejected As indicated before the same difficulty arises in connection with prognostic stratification of the patients which was also rejected for other reasons

The method of allotting patients found on careful consideration to be the best was to let the question of which group a patient was included in depend on to which department he was admitted This method could be used as nearly all the patients with acute myocardial infarction were admitted to hospital as emergencies Such admissions occur in the same way in all the municipal hospitals in Oslo The doctor wanting the admission contacts a ***hospital bed service outside the hospital*** This agency is given the number of empty beds in each of the three medical departments every day Between 8 am and 7 pm they decide to which department an emergency shall be admitted From 7 pm until 8 am the next morning the patients are admitted alternately to the three departments so that the night work is shared between their staff *

Question of the use of placebos

In many of the recent controlled clinical therapeutic trials the well known placebo technique sometimes in the form of a double blind test has been used

The question of a placebo treated control group was also considered in this investigation but was rejected for the following reasons the use of placebos would mean that all the patients in the control group would have to attend clinics regularly every 1–3 weeks have a venepuncture and on a fictitious basis get a given dose of the placebo This would have to go on for several years How far a doctor even with an ideal motive is justified in interfering in the life of a patient and fellow being is a very difficult question both from the ethical and legal points of view This investigation was carried out by one individual and a double blind test with the possible additional certainty of placebo treatment was therefore impracticable The ethical side of the question also thus comes into sharper relief as the responsibility for the additional load on the patients would rest on the author personally One cannot help thinking of the demoralising effect if for years a doctor has to act to his patients and knowingly deceive them

(The only exception to th[illegible] ar[illegible] a f[illegible] patients referred directly by the physicians in the departments Numerically such patients were very few There is also no reason to suppose that patients with acute myocardial infarction in this category would vary from department to department)

On the other hand it is doubtful whether use of placebos would give very much safer results in an investigation like the present one The first things to be compared in this investigation are objective phenomena such as the occurrence of recurrent infarcts and the number of deaths in the two groups Such phenomena hardly depend on suggestion or on the subjective feelings of the patient

The precautions taken so that the patients in the treated and control groups would have as similar cardiological treatment and supervision as possible apart from the use of anticoagulants will be discussed in more detail later

Age limit

Very old patients are usually frail and find it difficult to get about so it is often impossible for them to attend the out patient clinics It was therefore decided to limit this investigation so that it only included patients who were not yet 76 years old when admitted for their acute infarct

Size of treated and control groups

In a controlled clinical trial it is usually best if the groups to be compared are of approximately the same size The method of allotting patients used in this investigation made it necessary for this question to be considered As mentioned the patients were from three equally large medical departments each with about 150 beds The number of patients treated every year for acute myocardial infarction varied slightly in the different departments for the following reasons Dept IX is the only one which treats patients with pulmonary tuberculosis and such patients occupy about 40 of their beds Depts VII and VIII are more similar as both are general medical wards During this study however metabolic and digestive system diseases tended to be the main interest in Dept VII while cardiovascular diseases were the main interest in Dept VIII This lead to a certain moderate bias in the type of cases admitted This fact will be illustrated by the following figures for the number of patients under 76 years old with acute myocardial infarction in each department who in 1949 (the year before the investigation was planned) survived their acute attack by more than one month Dept VII 41 patients Dept VIII 47 patients and Dept IX 28 patients Total 116 patients It was therefore decided to allot the patients to the treated and control groups in the following way for all the patients admitted to Dept VII anticoagulant therapy would be stopped after one month and the patients assigned to the control group All the patients in Dept VIII would get long term anticoagulant therapy The patients admitted to Dept IX would for alternating periods of about half a year be treated either as patients in Dept VII and assigned to the control group or as patients in Dept VIII and assigned to the treated group Dept IX would be told when to change treatment by the investigator who tried to make the groups as equally sized as possible

Patients who had to be withdrawn from the final investigation

When the investigation was planned it was clear that some of the patients who satisfied the requirements mentioned would not be able to go through with the regular out patient control It was reckoned that patients would have to be withdrawn for the following main reasons (1) Severe clinical heart failure (2) Severe complicating disease with a bad prognosis or very reduced mobility (3) Mental disease or severe psychic debility (4) Contraindication to use of anticoagulants (5) Geographical conditions (6) A combination of these factors or others giving rise to reduced mobility or complete invalidism

The patients in the control group who for the same reasons would not have been able to have had out patient treatment with dicoumarol also had to be rejected The question of exclusion from the investigation was usually taken up with the doctors in the appropriate department who knew most about the patient The final decision was however made by the investigator with the above factors in mind The number of such cases and the reason for their exclusion will be mentioned later

Clinical investigation of the patients while in hospital

For any clinical study which is planned to start by collecting patients who will be subsequently under observation for some time it should be possible for the investigation of each individual case to be the same All those who have attempted clinical follow up studies on the basis of old case histories know how disheartening it is to hunt in vain for important information In the present study an effort was therefore made so that all the patients should have the same clinical investigations as far as possible right from the time of admission It was borne in mind that the patients would be from 3 different medical departments and that many different doctors would take part in the examination of the patients and the taking of case histories The author considered that the clinical investigations required should not be so numerous and time consuming that it might be difficult to carry them out They should therefore not be too different from those normally carried out in the 3 departments on a patient with acute myocardial infarction

At the start of the investigation the following schedule was worked out for the medical investigation of the patients and issued to the relevant doctors

Case history

The case history must as far as possible contain information about previous (1) hypertension (2) angina pectoris (3) infarction (4) prodromal symptoms of infarction (5) heart failure and (6) whether the present infarct occurred when the patient was resting or exerting himself

Clinical examination

The clinical examination must include looking for (1) pericardial friction (2) gallop rhythm (3) signs of shock (4) signs of heart failure (dyspnoea cyanosis congestion of the liver peripheral oedema) and (5) signs of xanthomatosis (xanthomatous nodules and xanthelasma)

Investigations

The following *investigations* must be carried out on all patients (1) pulse counted every morning and evening (2) temperature taken every morning and evening (3) blood pressure taken daily the first 3 days thereafter once a week (4) electrocardiogram to be taken in the first days as often as necessary for diagnosis and treatment and again just before discharge (5) height (6) body weight and (7) X rays of the heart to determine cardiac volume before discharge

Laboratory investigations (1) white blood cell count on the first 3 days (after admission or after the attack) (2) BSR on the 1st 3rd and 5th days and later once a week (3) fasting blood sugar the day after admission (infarct) (4) serum cholesterol and (5) PP value of blood before anticoagulant therapy started

This schedule was considered to contain the minimum requirements and was naturally supplemented if the diagnosis or more especially the treatment made it *necessary*

A similar but rather more simple schedule was duplicated and issued to the nurses in the 3 departments and kept handy in each ward The senior nurses also attended a meeting where the most important features of the investigation were gone through in more detail and the significance of a complete investigation was emphasised

In order to make it even more simple forms were made to hang on the back of the temperature charts of all patients with certain or probable acute myocardial infarction showing the tests to be carried out so that they could be crossed out as they were done Finally a schedule was sent to the laboratory staff which informed them when an infarction patient was admitted and reminded them which laboratory investigations should be carried out while the patient was in the ward

This regime worked very well and made certain that the patients had a fairly uniform investigation as will appear later

Diagnosis of the acute infarct—diagnostic criteria

The primary requirement before the patients could be included in this investigation was that while in hospital they should have definite signs of *a recent acute myocardial infarct* All cases in which the diagnosis was in doubt were excluded an no case was included unless the doctor in charge of the daily treatment and the investigator agreed on the diagnosis The diagnostic criteria used to make the diagnosis were the usual ones

(1) Attack of pain of typical character and localisation
(2) Typical electrocardiographic changes which gradually alter during the course of the disease
(3) Pericardial friction rub
(4) Raised temperature
(5) Leucocytosis the first days after the attack
(6) Increasingly raised BSR the first days after the attack
(7) Considerable fall in blood pressure the first days after the attack
(8) Signs of shock paleness sweating feeble rapid pulse and severe fall in blood pressure
(9) Tachycardia with a pulse rate of 90 or more the first days after the attack
(10) Signs of left heart failure with dyspnoea clinical (and/or radiological) signs of pulmonary congestion and possible pulmonary oedema
(11) Raised fasting blood sugar during the first 24 hours after the acute attack

There was no doubt about the diagnosis from the clinical investigations in any of the cases included in the clinical trial That the diagnostic criteria were strict enough is demonstrated by the fact that signs of previous infarction were present in all the 43 patients who later came to post mortem

Investigation technique

The laboratory investigations carried out while the patients were in hospital were done in the clinical laboratories attached to each of the 3 departments During the follow up of the patients these investigations were all done in Dept VIII Some of the techniques used are described below

Quantitative estimation of prothrombin proconvertin Owren s PP method

The quantitative estimation of prothrombin was carried out using Owren s PP method which really estimates *the combined effect of prothrombin and proconvertin* The method was originally described by *Owren* in 1947 (pp 265–271) It was later slightly modified see *Owren* (1949) and *Owren and Aas* (1951) The theoretical basis for the method and its theoretical and practical advantages have previously been discussed in more detail in this paper (see pp 27–29)

The method was introduced by the author into the 3 medical departments in Ulleval Hospital in the spring and early summer of 1950 All the details of the method were supervised and the laboratory nurses in the 3 departments were trained in the technical details by the author personally The thromboplastin extract and the prothrombin and proconvertin free ox plasma reagents on which the method is based were produced by the author in the clinical laboratory of

Dept VIII and the chemical reagents by the central laboratory for medical physiological chemistry in Ullevål Hospital The method used for extraction of the reagents was as follows

Thromboplastin

Thromboplastin was extracted from human brain in the following way the brain was freed from pia and blood vessels and the blood washed off under cold running water Next suitable bits were macerated and finely divided for 1½–2 minutes in an Ato mix (blender) with a solution of 0 9 % NaCl For a whole brain 1½–2 litres NaCl solution warmed to about 40° C were used The emulsion stood for 1–2 hours after which it was centrifuged for at least 15 mins at 2 500 r p m The extract was then decanted and the deposit thrown away

The activity of the thromboplastin was tested in the following way Parts of the extract were diluted (1 1 1 2 and 1 3) with physiological saline and the prothrombin complex time of normal plasma was estimated using Quick s method (0 2 ml brain extract + 0 2 ml normal plasma were mixed in a test tube put in a water bath at 37° C and then recalcified with 0 2 ml 25 mM $CaCl_2$ solution at the same temperature) Depending on the results of this test all the extract was diluted to the lowest concentration which gave optimal activity During the final dilution Owren s buffer corresponding to 10 % of the whole extract was added as well as physiological saline The final extract was put in small tubes in amounts needed for daily use and stored at –20 C

Prothrombin free and proconvertin free ox plasma

Ox blood (9 volumes) was bled straight into 1 volume 2 5 % (w/v) potassium oxalate (monohydrate) and mixed at once The oxalated blood was centrifuged at 2 500 r p m for about 15 mins The plasma was then pressure filtered through a clarifying filter containing 20 % asbestos and then twice through a filter containing 30 % asbestos (If a filter containing 50 % asbestos instead of 30 % is used after the initial clarifying filtration one filtration will usually be sufficient)

The following test was carried out to make certain that the plasma no longer contained prothrombin or proconvertin after filtration 0 2 ml ox plasma + 0 2 ml thromboplastin were mixed in a test tube placed in a water bath at 37° C and then recalcified with $CaCl_2$ solution (about 35 mM) (see later) If the coagulation factors mentioned were absent the mixture would not coagulate If it did coagulate the plasma was re filtered through the 30 % asbestos filter In practice it was stipulated that the mixture should stand for at least 20 mins without coagulating By adding 0 5 N HCl the plasma pH was adjusted to 7 35 with a glass electrode When ready the plasma was put in small tubes in the approximate amounts needed for daily use and stored at –20° C

Owren's buffer

has the following composition

Sodium diethylbarbiturate	11 75 g
NaCl	14 67 g
HCl 0 1 N	430 ml
Distilled water to	2 000 ml

The pH was controlled and adjusted to 7.35 with a glass electrode

The plasma dilution fluid

has the following composition

Potassium oxalate (monohydrate) 0 7 %	100 ml
Owren's buffer	200 ml
NaCl 0 9 % to	2 000 ml

Original CaCl solution

About 100 g calcium chloratum sicc pro analysi was dissolved in 1 000 ml distilled water The concentration of calcium was determined by estimating the concentration of chloride The solution was then diluted to *500 mM*

CaCl solution for optimal recalcification

The calcium chloride concentration for optimal recalcification was determined experimentally for each new supply of ox plasma The method was as follows the original solution of 500 mM CaCl was diluted to 50 mM with distilled water By further dilution with Owren's buffer calcium chloride solutions of 20 25 30 35 40 45 and 50 mM were made Each of these were tested (double tested) against a normal plasma in Owren's system (see below) The optimal calcium chloride concentration is that which gives the shortest coagulation time in the system and this was used for the ox plasma A solution containing 35 mM CaCl was usually the optimal one

Practical technique in estimation of PP values

4 5 ml blood was aspirated by venepuncture into 0 5 ml 2 % (w/v) potassium oxalate (monohydrate) in a 5 ml record syringe and mixed immediately The oxalated blood was then centrifuged and 0 2 ml plasma was diluted with 1 8 ml plasma diluting fluid The concentration of oxalate in the diluted plasma was 100 mg %

0 2 ml of the prothrombin and proconvertin free ox plasma were mixed in a small serological test tube with 0.2 ml thromboplastin and 0.2 ml of the diluted plasma The mixture was put in a water bath at 37° C for 5 mins It was then recalcified with 0 2 ml of the optimal CaCl solution and the coagulation time found in the usual way with a stop watch

The coagulation time in this system depends on the combined effect of prothrombin and proconvertin in the plasma investigated It was expressed as a percentage of the normal with the help of a correlation curve The curve was made as described by *Owren* (1949) by estimating the coagulation time of increasing dilutions of normal plasma These dilutions were made of the normal 10 % dilution by using a diluting fluid like that given above but with 100 mg % potassium oxalate (instead of 70 mg %) to obtain a constant concentration of oxalate in all dilutions On double logarithmic paper with the dilutions expressed as percentages as the abscissa and the time in seconds as the ordinate the correlation curve approaches a straight line The standard solution (10 %) of normal plasma represents 100 % The PP value of the plasma investigated is read off as a percentage of the normal value

The normal standard was determined as the average of 10–20 normal blood samples and was controlled at intervals to make certain that the value remained constant When a new correlation curve was introduced (a new one must always be made before starting to use a new supply of ox plasma or new thromboplastin extract) it was made certain that the values in the old and new coagulation systems corresponded accurately by comparing a number of samples in the two systems Frozen standard plasma was also occasionally used as control to make even more certain that there were no changes in values especially when changing to a new correlation curve

All the PP values in the present investigation were double tested

The samples of blood were investigated immediately after they were taken (the only exceptions being a few samples from 4 patients when they were away on business or holiday) Neither addition of a small amount of heparin (to stop activation of proconvertin) nor mercaptol (to prevent damage by bacteria) as recently recommended by *Owren* (1954) was therefore considered necessary (see p 29)

Serum cholesterol estimation

The total serum cholesterol was estimated as described by *Kingsley and Shaffert* (1949) without saponification As is known cholesterol esters give a stronger colour in the Liebermann Burchardt reaction than free cholesterol This is corrected for by multiplying the values found by the factor 0 84

Liver function tests

In order to see whether prolonged use of dicoumarol had any demonstrable effect on the liver function the following tests were carried out on all the patients in the treated group

Icterus index (Meulengracht)

Thymol turbidity test (Maclagan 1944)

Gros test as modified by Stolte *(Gros* 1939 *Christoffersen and Raagaard* 1947)

Fractional estimation of *serum albumin and serum globulin (Houe* 1921)

Electrocardiographic technique

The technique for taking electrocardiograms used in the three medical departments during the investigation was registration of the 3 standard extremity leads and IV F If however myocardial infarction was suspected these were supplemented by the praecordial leads IV R and CF Frequent electrocardiograms in the first and second week after an acute attack were considered especially important partly because the gradual changes during the course of the disease could thus be followed and partly so that the relatively late changes which may confirm the diagnosis of an infarct after an acute attack of praecordial pain would not be missed Unipolar leads were only used exceptionally

Radiological examination of the heart

Radiological examination of the heart was in all the patients in this investigation carried out using *Jonsell s* modification (1939) of *Liljestrand Lysholm Nylin and Zachrisson s* method (1939) which is based on Rohrer–Kahlstorf s formula for determining the cardiac volume See *Rohrer* (1916) and *Kahlstorf* (1932) The examinations were performed in the Roentgen Department in Ulleval Hospital (Head Dr J Frimann Dahl M D) All the X rays were examined and measured by Dr Per Amundsen *Amundsen* (1956) has shown that the errors in radiological estimation of the heart volume are considerably reduced if the measurements are all made by the same trained observer The reader is referred to the same author for more details of the radiological technique

Summary and conclusion

The following subjects have been discussed in this chapter (1) Allotting patients to treated and control groups (2) Clinical investigation of the patients while in hospital (3) Criteria for the diagnosis of the acute infarct (4) Special investigations used (laboratory techniques electrocardiograms and radiological examination of the heart)

It has been shown that neither the author the doctors referring the cases nor anyone else who might have a subjective point of view have had an opportunity of influencing the distribution of the patients between the two groups to be compared *An exception from this was however the patients* in the treated group in whom for different reasons long term therapy was impossible and the corresponding patients in the control group all of whom had to be excluded from the investigation This exclusion was done by the author usually in consultation with other doctors and according to uniform principles which had been previously laid down Subjective selection was thus prevented

The final result of allotting the patients to the treated and control groups will be illustrated and discussed in connection with the statistical comparison of the

two groups which was considered as a necessary background for evaluating the results The excluded patients will also be discussed in more detail later

The possibility of using placebos in the control group was considered but rejected for ethical and legal reasons

Details are given of the schedule drawn up for the clinical investigations while in hospital and the measures taken to ensure that all the patients had as similar investigations as possible

Finally the most important special investigation techniques are mentioned and more details are given of the method for determination of prothrombin proconvertin Owren s PP method which plays an important part in this investigation

CHAPTER V

Selection of patients for the investigation

The total material—section A

The raw material for this investigation (designated section A) consisted of 277 consecutive patients treated for acute myocardial infarction in Ulleval Hospital Departments VII VIII and IX in the period July 1950 to July 1953 They were all under 76 years old on admission

According to plan the use of anticoagulants in the control group should be discontinued after a maximum of 1 month this therefore marks the beginning of the true observation time for the controlled therapeutic trial No patient was therefore included in this investigation (either in the control or treated group) unless he survived for the first month of treatment + the period from the acute attack to the commencement of treatment It was also stipulated that the latter period should not exceed 1 month It can therefore be stated that the 277 patients who provided the raw material for this investigation had all survived their acute infarcts by between 1 and 2 months when the observation time started Further details concerning the interval between the acute infarct and admission to hospital are shown in Table 19 page 70

Of the 277 patients in section A 138 were assigned to the treated and 139 to the control group The principles followed for inclusion in one or other group are referred to in Chapter IV *

The inclusion of patients in the investigation was originally stopped on the first of April 1953 when there were 261 patients However in the period from the middle of May to the middle of July 1953 16 additional cases were included The reason was that in the daily press a great deal of publicity was given to the question of long term treatment with anticoagulants in cardiovascular disease One therefore had to reckon with the possibility that many of the patients in the control group would desire this form of treatment and possibly deplete the control group Even if this did not happen it would be an advantage to have a larger number of cases in the investigation

The only exception from this was the selection of the first 10 patients who were all admitted to Dept VIII where the investigation was first started These were divided between the treated and control group by allotting patients to different groups on odd and even dates of admission

These last 16 cases consisted of 7 consecutive patients from Dept VIII who were included in the treated group and 9 consecutive patients from Dept IX who were included in the control group *

Patients excluded from the controlled clinical trial according to plan

As mentioned earlier it was reckoned that some of the patients originally included would not be able to carry through the regime necessary in ambulant anticoagulant therapy See page 47

Of the 138 patients in the treated group there were 6 men and 6 women who were not able to undergo this form of treatment and who therefore had to be excluded from the investigation

TABLE 4

Patients who had to be excluded from the treated group because they could not have undergone long term ambulant treatment with anticoagulants and those excluded from the control group because they could not have undergone such treatment had they been in the treated group

Reason for exclusion	No of patients Treated group	Control group
I Severe heart failure	1	2
II Immobilising disease of skeletal muscle or nervous system		
(1) Chronic rheumatoid arthritis	1	1
(2) Advanced arthrosis of hip and spine	1	1
(3) Hemiparesis after cerebral accident		1
III Mental diseases or severe psychic debility		
(1) Acute psychosis	1	
(2) Depressive psychosis transf to psy dept	1	
(3) Mental defective	1	
(4) Senile dementia (cerebral arterioscl.)	1	
IV General physical and psychic deterioration because of age and arteriosclerosis—combined with heart failure and/or angina pectoris	1	4
V Serious complicating condition with bad prognosis (anticoagulants possibly contraindicated)		
(1) Pulmonary tuberculosis with cavitation		1
(2) Renal tuberculosis with cavitation		1
(3) Renal disease with uraemia + advanced aortic valvular disease (luetic)		1
(4) Diabetes mellitus with advanced nephropathy and retinopathy + polycythaemia vera		1
VI Geographical conditions		
(1) Living in another part of the country	3	
(2) Living abroad	1	1
Total number of patients who had to be excluded at the outset	12	14

* These last patients in the control group were all from Dept. IX because the doctors in Dept VII had started long term treatment in some cases of infarct in April 1953

Of the 139 patients in the control group there were 6 men and 8 women who would not have been able to undergo continuous ambulant treatment with dicoumarol if they had been in the treated group. They therefore also had to be excluded.

The reasons for these patients being excluded are shown in *Table 4* and it is clear that in all cases these reasons were very weighty. In fact it was only insurmountable obstacles that were accepted as reasons for exclusion.

It is stated in many publications on long term treatment with anticoagulants that only intelligent and co-operative patients were chosen for this form of treatment. No such selection was made here. It was thought first of all that such a selection could bias the investigation and reduce its dependability. Secondly it was considered that the amount of intelligence required can be reduced to a minimum if the technique at the follow-up clinics and the dose regulation is given careful consideration. On the basis of personal experience it was also thought that the necessary regime provides opportunities for supervision and for influencing and increasing the patient's co-operation.

After exclusion of the patients mentioned above the group of patients for the controlled clinical trial was reduced from 277 to 251 of which 126 were in the treated and 125 in the control group.

Additional patients excluded from the controlled clinical trial

The group of patients for the controlled investigation was however further reduced for different reasons outside the influence of the investigator.

Of the 126 patients after primary exclusion in the *treated group* there were 7 cases (3 men and 4 women) who were also eliminated from continued treatment with anticoagulants. The reasons for this are shown in *Table 5*. It will be seen that in 4 of these 7 cases the reason was that the patient himself did not want continued treatment and supervision after discharge and in 1 case it was because of progressive dementia leading to an inability to keep to the dosage prescribed so that the control became illusory. In only 2 cases was treatment stopped as a result of haemorrhagic conditions and established contra-indication to continued treatment with anticoagulants. One of these cases was a 66 year old man in whom after 3 months ambulant treatment anaemia and blood in the stools were demonstrated. The bleeding continued after the PP value had become normal. As thorough clinical and radiological investigation were not able to demonstrate the primary cause of the bleeding an exploratory laparotomy was carried out which showed haemangiomatosis in the mid part of the small intestine for a length of about 1½ metre. Resection was not performed and continued treatment with anticoagulants was considered to be contra-indicated. The other case was a 60 year old man with essential hypertension (B.P. 230/100–240/115) and signs of advanced arteriosclerosis. After 12½ months treatment with satisfactory control he deve-

TABLE 5

Patients who had to be excluded from the *treated group* because of obstacles to the execution or completion of the treatment planned

Reason for exclusion	No of patients
I Did not wish continuous treatment with anticoagulants	
(1) Refused venepuncture while in ward took own discharge	1
(2) Did not wish treatment with anticoag after discharge	1
(3) Broke off amb tr after 2 months	1
(4) Neurosis after 3 months wanted to go back to previous doctor for treatment	1
II Progressive dementia did not succeed in keeping to dosage Treatment stopped after 9 months—unsatisfactory control	1
III Haemorrhagic conditions Established contra indications for continued treatment	
(1) After 3 months amb tr —anaemia and occult bleeding Laparotomy intestinal haemangiomatosis	1
(2) Severe essential hypertension After 12 months amb tr cerebral haemorrhage with transitory left hemiparesis (PP value 37 %)	1
Total number of patients	7

loped a cerebral haemorrhage with transitory left sided hemiparesis The PP value estimated 3 hours after the onset was 37 % It was considered that his hypertension and arteriosclerosis were the primary causes and the use of anticoagulants a contributory cause of bleeding Continued treatment was considered to be contra indicated

Of the 125 patients after primary exclusion in the *control group* there were 7 cases (4 men and 3 women) who had to be eliminated as they later fell below the standard for patients in the control group The reasons for this are shown in *Table 6* It will be seen that 1 patient was difficult refused treatment especially venepuncture and took her own discharge It would have been impossible to give

TABLE 6

Patients who had to be excluded from the *control group* either because long term anticoagulant therapy was started or because they would have been excluded had they been in the treated group (1 case)

Reason for exclusion	No of patients
I Refused venepuncture while in ward took own discharge	1
II Treatment with anticoagulants started	
(1) By the investigator by special request	1
(2) By other doctors or hospitals	5
Total number of patients	7

her continued anticoagulant therapy and she therefore had to be excluded although she was in the control group Five patients had to be excluded because

continuous anticoagulant therapy was subsequently started by doctor in other hospitals In 1 patient who was a doctor employed in the hospital treatment with anticoagulants was continued by the investigator by special request

On account of the above mentioned secondary reasons for exclusion the group of patients for the investigation was reduced further from 251 to 237 cases of which there were 119 in the treated and 118 in the control group These patients provided the basis for the controlled clinical trial and has been termed *section B*

Summary

In this chapter the size of the raw material—section A—has been reported on The patients included were all under 76 years old they were admitted to one of the three medical departments and had survived a definite episode of acute in farction Next the number of patients in each group is mentioned who according to the plan of the investigation had to be excluded either becau e they were not able to undergo the necessary out patient control and treatment or for other reasons Finally a very few patients had to be excluded because for reasons outside the influence of the investigator they did not satisfy the requirements for the investigation Section A consisted of 277 cases and it was thus reduced forming section B to 237 cases 119 in the treated group and 118 in the control group These cases formed the basis for the controlled clinical trial

CHAPTER VI

More details about the material
Statistical examination of the comparability of the treated and control groups

In this chapter the composition of the material for this investigation will be examined more closely especially to assess the comparability of the treated and control groups at the beginning of the investigation

If it had been possible to assign the patients to the groups merely by drawing lots this assessment of comparability would be superfluous from a theoretical point of view As this was not possible it is necessary to make a statistical analysis to see whether the distribution of the patients is biased in any way It must be known whether or not the method of selection used has given a chance distribution in other words whether the differences between the groups are no greater than would be found if lots had been drawn

In order to make this comparison the distribution of various general and special characteristics of the material will be examined This will be shown in the tables given below In most of these tables not only the reduced material—section B the basis of the controlled clinical trial but also the complete unreduced material section A will be tabulated This has been done so as to see whether the exclusion of patients referred to in the previous chapter has biased the composition of the material

When comparing the distributions in the two groups two common statistical methods to test the agreement between the two distributions have been used namely *Karl Pearson s chi square goodness of fit test* and *Student s T test*

The hypothesis that the differences between two distributions only depend on chance so that the groups are comparable is usually termed the *null hypothesis* In this investigation a *level* of 5% was chosen giving a certain range of chance variations If the observations fall outside this range the null hypothesis is rejected i e it is assumed that there is a systematic difference in the distribution By using a level of 5% it has been made certain that there is *only' a 5% probability that chance differences will be interpreted as systematic* The standard test methods mentioned above are universally used as they seem to provide a satisfactory basis for the conclusion

General characteristics of the sample

Age distribution

The ages given below are the ages on the last birthday on admission with the acute infarct *The age distributions in men and women are shown in Tables 7 and 8 Table 9* shows the average ages

TABLE 7

Section A Age and sex distribution in the treated group and control group

Age group years	Men		Women	
	Treated	Control	Treated	Control
30–39	1	4	0	0
40–49	15	16	1	0
50–59	39	37	9	16
60–69	33	30	21	9
70–75	9	16	10	11
Total no of cases	97	103	41	36

TABLE 8

Section B Age and sex distribution in the treated group and control group

Age group years	Men		Women	
	Treated	Control	Treated	Control
30–39	1	4	0	0
40–49	15	14	1	0
50–59	37	33	7	12
60–69	27	29	20	7
70–75	8	13	3	6
Total no of cases	88	93	31	25

TABLE 9

Sections A and B Average ages in the treated group and control group

Material	Average age in years					
	Men		Women		Both sexes	
	Treated	Control	Treated	Control	Treated	Control
Section A	58	58 5	64 6	62 8	60	59 6
Section B	57 6	58 5	63.3	62 0	59	59.2

The age distributions for men and women in Table 7 and 8 are compared using the chi square test of homogeneity Only in women in section B is the proba

bility for a chi square value larger than that observed under the null hypothesis < 5% (3%) By combining the tests for men and women in section B Prob (chi square > obsv) = 9 5 % On the whole the figures must be considered to be within the range of chance variations There is therefore no reason to reject the null hypothesis

The difference between the average ages for men and women in the treated and control groups sections A and B in Table 9 is *not significant*

Sex distribution

The sex distribution is shown in *Tables 7 and 8* The chi square goodness of fit test showed no significant difference between the groups either in section A or B In section A the sex ratio men/women = 2 6 1 and in section B 3 2 1 The last distribution corresponds to that found by *Wright Marple and Beck* (1954) i e 3 3 1

Race

With very few exceptions (see below) the patients in this investigation were inhabitants of Oslo which consists chiefly of people of Nordic extraction with traces of Alpine and Baltic elements Further in section A there were 2 Jews in each group and in section B 1 Jew in the control group

Geography

Five patients in section A who were only temporarily in Oslo had to be excluded from section B (see Table 4 p 56) One patient in the treated group who lived about 100 km from Oslo was able to attend the follow up clinics regularly and was therefore not excluded In section B there were 3 patients in the control group and 1 in the treated group who later moved away from Oslo but even so they were able to be under continued observation All the other patients lived permanently in Oslo during the observation period

Social standing

Table 10 shows the distribution of the male patients in the different social groups The classification is in agreement with that used in the Norwegian National Census in 1946 The definitions in this publication have been followed as closely as possible Retired patients and others without permanent work due to age or illness before admission were classified according to previous work and social standing

The agreement between the distributions is very good There is no significant difference The distribution agrees well with that found by *Westlund and Hougen* (1956) for male infarct patients in Oslo

TABLE 10

Social standing

Social group	Section A Treated	Control	Section B Treated	Control
Independent business	12	15	11	14
Independent skilled worker	1	2	0	1
High grade employees	7	6	6	6
Office and shop employees	15	14	15	13
Craftsmen	19	18	18	14
Foremen	3	5	3	4
Labourers	40	43	35	41
Total no. of cases	97	103	88	93

Height and weight

Tables to show each individual patient's height, weight and height weight relationship according to Broca's formula [weight (kg) – (height – 100) (cm)] as used in the statistical analysis have been omitted to save space.

Table 11 shows the average weights for men and women in sections A and B in the treated group and control group and the average values in section B for the height weight relationship according to Broca's formula.

TABLE 11

Average weights and height weight relationships

	Section A		Section B		
	No. of cases investig.	Average weight kg	No. of cases investig.	Average weight kg	Average height weight rel. (Broca)
Men Treated group	97	72.16	88	72.95	0.068
Men Control group	103	73.08	93	73.47	1.753
Women Treated group	39	65.48	31	65.69	7.32
Women Control group	35	66.05	25	66.72	6.60

Three women in section A left the hospital before their heights and weights could be measured.

The average weights and average values for the height weight relationships (Broca) for men and women in section B were compared using Student's T test. The weight differences and differences between the average values for the height weight relationships in the treated group and control group are not significant.

Owren (1945) has published tables to show the average weight in relation to the height in Norwegian men and women in the age groups between 20–54 years. If his figures are compared with those for the men there is no noticeable dif

ference but the women in the present investigation on the whole are 2–3 Kg overweight

In section B the following numbers of patients were *overweight* by 10 Kg or more in accordance with Broca's formula men 14 in the treated and 16 in the control group women 14 in the treated and 6 in the control group The following were 10 Kg or more *underweight* men 12 in the treated and 11 in the control group women 1 in the treated and 2 in the control group Therefore amongst the men in this investigation there were almost as many thin as obese patients whereas there was a preponderance of obese patients amongst the women A general impression of this is shown in the average height weight relationship in the two sexes (Table 11)

The following of the above mentioned statistical tests were combined chi square goodness of fit test for ages of women in section B T test for weights of men in section B T test for weights of women in section B and chi square goodness of fit test for social standing of men in section B There was no significant difference

On the whole the information about age weight and social standing give *no basis for a rejection of the null hypothesis*

Conditions in the previous history considered to be of significance for the prognosis

Previous angina pectoris

Angina pectoris included patients with typical pain which had started more than one month before the infarct Attacks which appeared for the first time during the month before the attack were reckoned as *prodromal symptoms*

The distribution of the patients with previous angina pectoris is shown in *Table 12* Using the chi square goodness of fit test there is no significant difference

TABLE 12

Previous angina pectoris

	Section A		Section B	
	Treated	Control	Treated	Control
Previous angina pectoris	66	76	57	66
No previous angina pectoris	72	63	62	52
Total number of cases	138	139	119	118

Previous myocardial infarction

Table 13 shows the number of patients who had had one or more attacks of verified or probable acute myocardial infarction before the attack which included them in the investigation Verified infarcts included cases where the diagnosis of

TABLE 13

Previous infarction

	Section A Treated	Section A Control	Section B Treated	Section B Control
Previous infarction	18 + (2)	13 + (3)	15 + (1)	10 + (1)
No previous infarction	118	123	103	107
Total number of cases	138	139	119	118

The number in brackets refer to probable but not verified case

acute myocardial infarction was made by clinical and electrocardiographical examination either during a previous admission to hospital or when visiting a specialist and where these data were available for the author Probable infarcts included cases where there was a good case history indicating a previous infarction but where objective data to verify the diagnosis were not available

In the treated group there was 1 patient in sections A and B who had had 3 certain previous infarcts In the control group there were 2 patients in section A and 1 in section B who had had 2 such attacks before

The distribution of the patients who had had previous infarcts was investigated using the chi square goodness of fit test There was no significant difference It should however be noted that there was a preponderance of such cases in the treated group (in section B 16 cases treated and 11 control) which makes the prognosis worse in the treated group

Table 14 shows the number of patients in each group who had had previous coronary disease either angina pectoris or acute myocardial infarction or both The chi square goodness of fit test shows that there is no significant difference in the distribution

TABLE 14

Previous angina pectoris and/or myocardial infarction

	Section A Treated	Section A Control	Section B Treated	Section B Control
Previous angina pect and/or infarct	72	77	62	66
No prev angina pect and/or infarct	66	62	57	52
Total number of cases	138	139	119	118

Previous hypertension

Exact information about the previous blood pressure was only present to a limited extent in this investigation However in many of the patients especially if they had been in hospital before the results of one or several readings were available If these measurements had shown a diastolic blood pressure of 100 mm Hg or more and/or a systolic pressure of 160 mm Hg or more it was considered

that the patient had had hypertension A few patients were able to state that they had had a blood pressure of 180 mm Hg or more These cases were also included in this group as it was considered that a doctor would not give a patient such information unless there was a considerably raised blood pressure

Table 15 shows the distribution of the available data in men and women in the material A chi square test of homogeneity showed no significant differences between the groups either in section A or B

It is shown that previous hypertension was much more common amongst the women than the men in this investigation Amongst the cases where information was available hypertension occurred in about 90 % of the women and barely 50 % of the men This was probably the reason that information about previous blood pressure was available far more often in the women than the men as shown in the table The relationship between sex and previous hypertension in patients with acute myocardial infarction has been shown previously by many authors including *Master Dack and Jaffe* (1939) *Mintz and Katz* (1947) *Doscher and Poindexter* (1950) and *Wright Marple and Beck* (1954)

TABLE 15

Previous hypertension

	Section A				Section B			
	Men		Women		Men		Women	
	Tr	Cont	Tr	Cont	Tr	Cont	Tr	Cont
Previous hypertension	30	26	31	25	26	25	24	20
No previous hypertension	32	36	4	2	30	33	3	1
Unknown	35	41	6	9	32	35	4	4
Total number of cases	97	103	41	36	88	93	31	25

Previous heart failure

Previous heart failure is an indication of persisting serious heart disease and is therefore of considerable prognostic interest By taking a careful history and on the basis of previous case histories the position was made as clear as possible Indications of heart failure were oedema nocturnal attacks of dyspnoea and advanced invaliding dyspnoea on exertion of certain cardiac aetiology Milder grades of exertion dyspnoea were not included because the pathogenesis is so often uncertain (emphysema obesity age etc)

Table 16 shows the distribution of previous heart failure and there is obviously no reason to reject the null hypothesis

Previous valvular disease

During admission for the acute infarct signs of valvular disease were found in some patients *Table 16* shows the number and distribution of these cases In the treated group aortic stenosis was diagnosed in 4 patients in sections A and B

In the control group valvular disease was demonstrated in 5 patients in section A of whom 3 were in section B Of the 2 patients who had to be excluded from section A one had syphilitic aortitis with aortic regurgitation combined with renal disease and uraemia and the other had aortic stenosis with severe clinical heart failure In section B there were two cases with aortic stenosis and one with rheumatic mitral and aortic valvular disease with radiologically enlarged heart but without signs of heart failure

TABLE 16

The number of patients who before the acute infarct had had heart failure *valvular disease cerebral vascular accidents obliterating arterial disease in the* legs or diabetes mellitus in the treated and control groups in sections A and B

Type of previous disease	Section A Treated (138 cases)	Section A Control (139 cases)	Section B Treated (119 cases)	Section B Control (118 cases)
Heart failure	10	9	8	7
Valvular disease	4	5	4	3
Cerebral vascular accident	7	5	5	4
Intermittent claudic	5	7	5	5
Diabetes mellitus	7	5	5	3

The distribution of the cases with valvular disease shows good agreement between the treated and control groups There is obviously no significant *difference*

Previous cerebral vascular accident

Table 16 shows the number and distribution of cases in which the past history or earlier case histories provided evidence of a cerebral vascular accident There is good agreement between the treated and control groups

Of the total 277 patients in section A there were 12 such cases (4 3%) which is in good agreement with the incidence reported by *Wright Marple and Beck* (1954)

Previous obliterating arteriosclerosis or thromboangiitis obliterans

It is a normal clinical experience that patients with coronary disease not infrequently show signs of peripheral obliterating arterial disease—and vice versa See for instance *McDonald* (1953) and *Selvaag* (1956)

No systematic clinical or radiological examination of the circulation in the legs was undertaken in this investigation Cases have only been recorded if the circulatory disturbance caused symptoms (intermittent claudication) which sometimes needed treatment

The distribution of these cases is shown in *Table 16* and shows very good agreement between the treated and control groups Of the total number of patients there were only 12 such cases (4 3 %) Two patients had thrombo angiitis obliterans The others all had obliterating arteriosclerosis

Six patients (3 treated and 3 control) all in section B had been treated for their arterial disease Lumbar sympathectomy had been carried out in 4 of these cases 2 in each group of whom 1 in each group had thromboangiitis obliterans In 1 patient in the control group section B the acute infarct developed in connection with the sympathectomy Three patients with obliterating arteriosclerosis 2 in the treated group section B and 1 in the control group section A (see below) had diabetes mellitus

Diabetes mellitus

The distribution of patients with previously diagnosed diabetes mellitus is shown in *Table 16* and there is clearly no significant difference between the treated group and control group In one case in the control group (see Table 4 p 56) advanced diabetes with complications was the main reason for excluding the patient from section B

Of the total number of patients there were 12 cases of diabetes mellitus (4 3 %) *Wright Marple and Beck* (1954) found an incidence of 11 %

Course of the recorded acute infarct

Information about the symptoms and signs observed during the acute phase of the infarct in this investigation will now be analysed The main object is still to investigate the comparability of the treated and control groups It will be seen whether there were systematic differences indicating that one or other group had more s rious infarcts and perhaps a worse prognosis

No attempt has been made to make criteria for grading the long term prognosis A grading has been suggested for the immediate prognosis by *Russek et al* (1951) and by *Schnur* (1953) Others maintain that it is very difficult to forecast the immediate prognosis after acute myocardial infarction and that attempts at grading are therefore of limited value See for instance *Halpern Lemberg Belle and Fichert* (1954) *Wright Marple and Beck* (1954) and *Holten* (1955)

It is probably even more difficult to grade the long term prognosis on the basis of criteria in the acute phase (see *Olsen Kahrs Rømcke and Lingjærde* 1956) In the present study the symptoms and signs have therefore been analysed individually as it was considered that this would provide equally good perhaps more objective information about the material and about the comparability of the treated group and control group

Prodromal symptoms of infarction

Prodromal symptoms of infarction are usually understood to be the development of preliminary angina like pain varying in type and intensity which may appear hours days or weeks before the major attack and can be a warning of impending acute infarction

The prodromal symptoms of myocardial infarction have previously been discussed by *Feil* (1937) *Sampson and Eliaser* (1937) *Plotz* (1944) *Yater et al* (1948) and others *Nichol et al* (1954) maintain that at least a third of all cases of acute myocardial infarction have preliminary angina like pain

Prodromal symptoms have included (1) the development of previously absent perhaps protracted and repeated angina like pain during the month before the acute infarct (2) a noticeable deterioration of previous angina of effort with more frequent longer and more intense attacks perhaps when at rest or asleep during the month before the infarct Attacks of pain which developed more than a month previously and which remained almost unchanged in character and intensity have been reckoned as angina pectoris (see p 64)

The distribution of cases with and without prodromal symptoms is shown in *Table 17* The chi square goodness of fit test for section A showed no significant difference In section B there is obviously no significant difference

Of the total 277 patients prodromal symptoms were observed in 109 cases (39 %)

TABLE 17

Prodromal symptoms of infarction

	Section A Treated	Section A Control	Section B Treated	Section B Control
Prodromal symptoms	59	50	50	49
No prodromal symptoms	79	89	69	69
Total number of cases	138	139	119	118

The beginning of the acute attack—at rest or on exertion?

An acute myocardial infarct not infrequently develops in relation to special circumstances such as unaccustomed exertion emotional excitement over eating or excessive consumption of alcohol In this investigation the problem has been simplified so as not to include all the details but it was attempted to ascertain whether the attack occurred on exertion or at rest

The distribution of the recorded data is shown in *Table 18* The chi square goodness of fit test showed no significant difference between the treated group and control group A relatively large number of the patients had their acute attack when at rest i e 176 of the total (approx 64 %)

TABLE 18

The beginning of the acute attack at rest or on exertion

	Section A		Section B	
	Treated	Control	Treated	Control
Attack at rest	84	92	72	78
Attack on exertion	50	42	44	35
Uncertain	4	5	3	5
Total number of cases	138	139	119	118

Interval between attack and admission.

Patients were not included in the investigation unless the interval between the acute attack and admission to hospital was less than 1 month (30 days) *Table 19* gives a general idea of how soon the patients were admitted to hospital with their acute attack It is seen that in section A 6 patients had their attack while they were in hospital and the information about the interval was uncertain in 7 cases Of the remaining 264 cases 145 (approx 55 %) were admitted within 12 hours 187 (approx 71 %) within 24 hours and 235 (approx 89 %) within the first 4 days

The distributions in the treated and control groups are in very good agreement No significant difference was shown with the chi square homogeneity test

TABLE 19

Interval between attack and admission

Interval	Section A		Section B	
	Treated	Control	Treated	Control
0– 6 hours	44	51	37	46
6–12 hours	27	23	23	16
12–24 hours	15	27	13	24
24–48 hours	14	11	14	10
2– 4 days	15	8	14	6
4– 7 days	7	6	7	6
1– 2 weeks	6	6	4	5
2– 3 weeks	2	1	1	1
3– 4 weeks	1	0	1	0
Attack in hospital	4	2	2	2
Uncertain	3	4	3	2
Total number of cases	138	139	119	118

Pain

No attempt has been made to grade the intensity or duration of the pain Such a grading would be of doubtful value partly because the patients subjective reaction to pain is so variable and partly because the grading might depend on several

TABLE 20

Pain

	Section A		Section B	
	Treated	Control	Treated	Control
Typical pain	126	131	113	113
Atypical pain	10	5	4	2
No pain	2	3	2	3
Total number of cases	138	139	119	118

different doctors subjective opinions It was therefore thought sufficient to ascertain whether or not the patients had pain with the development of the acute attack and if so whether it was typical in character and localisation

The results are shown in *Table 20* It is shown that only 5 of the 277 patients had no pain and that in a further 15 the pain was vague or atypical

The chi square goodness of fit test showed no significant difference in distribution between the treated group and control group

Vomiting

As vomiting frequently occurs with an acute myocardial infarct its occurrence was carefully recorded in this investigation No attempt was made to discover to what extent the vomiting observed might have been due to drugs especially morphine and other analgesics

The number and distribution of patients who had one or several attacks of vomiting is shown in *Table 21* The chi square goodness of fit test showed no significant difference between the treated and control groups It is shown that vomiting was observed in 125 of the 277 cases in section A i e 45 %

TABLE 21

Vomiting

	Section A		Section B	
	Treated	Control	Treated	Control
Vomiting	68	57	55	45
No vomiting	70	82	64	73
Total number of cases	138	139	119	118

Dyspnoea

Dyspnoea included cases who on examination had objective signs of dyspnoea and also cases where there was evidence of the development of considerable dyspnoea without simultaneous pain Subjective impressions of dyspnoea during the acute attack of pain were not included as patients so often confuse dyspnoea with the chest pain or the feeling of oppression that accompanies the pain

TABLE 22

Dyspnoea

	Section A		Section B	
	Treated	Control	Treated	Control
Dyspnoea	41	41	32	32
No dyspnoea	97	98	87	86
Total number of cases	138	139	119	118

Table 22 shows the number and distribution of cases with dyspnoea There is very good agreement between the treated and control groups In all dyspnoea was observed in 82 patients (30 %)

Heart failure

The number of patients who had a severe attack of acute pulmonary oedema is shown in *Table 23* There is good agreement between the treated group and control group Only 3 6 % of the patients in this investigation had such an attack *Wright Marple and Beck* (1954) found signs of mild moderate or severe pulmonary oedema in 27 % of their cases and moderate to severe pulmonary oedema in 8 % In the present study there was definite information only about the more severe cases The low percentage *is certainly partly due to this and* partly because patients who develop pulmonary oedema during the acute attack are usually the more serious cases so that many of them do not survive the first month

TABLE 23

Heart failure

The number of patients who during the first month of the course of the acute infarct developed signs of acute pulmonary oedema venous congestion enlarged liver peripheral oedema—or heart failure as shown by the presence of one or more of these signs

Clinical sign	Section A		Section B	
	Treated (138 cases)	Control (139 cases)	Treated (119 cases)	Control (118 cases)
Pulmonary oedema	4	6	3	4
Venous congestion	5	6	5	5
Enlarged liver	6	4	6	4
Peripheral oedema	12	15	11	10
Heart failure —all forms	23	22	21	16

Table 23 shows further that right sided heart failure in the form of *venous congestion* was observed in 11 cases (4 %) as an *enlarged liver* in 10 cases (3 6 %) and as *peripheral oedema* in 27 cases (approx 10 %) Finally at the bottom of the same table the number of cases in each group is shown who had heart

failure in the form of one or several of the 4 above mentioned signs (pulmonary oedema venous congestion enlarged liver and peripheral oedema) It is shown that 45 patients had this condition (16 %)

The chi square goodness of fit test was used on the distributions of the cases with peripheral oedema and heart failure and showed no significant difference between the treated group and control group There is obviously no significant difference for venous congestion and enlarged liver

Pericardial friction rub

The number of patients in whom a pericardial friction rub was heard is shown in *Table 24* and shows no significant difference between the treated and control groups with the chi square goodness of fit test This sign was found in 41 cases (15 %) *Wright Marple and Beck* (1954) found exactly the same incidence

TABLE 24

Pericardial friction rub

	Section A		Section B	
	Treated	Control	Treated	Control
Pericardial friction rub	21	20	20	14
No pericardial friction rub	117	119	99	104
Total number of cases	138	139	119	118

Gallop rhythm

Table 25 shows the number of patients in whom gallop rhythm was heard during the acute phase of the infarct The chi square goodness of fit test for section B showed no significant difference This sign was present in 25 patients (9 %) *Wright Marple and Beck* (1954) found gallop rhythm during the first week in 6 % of their cases

TABLE 25

Gallop rhythm

	Section A		Section B	
	Treated	Control	Treated	Control
Gallop rhythm	14	11	14	9
No gallop rhythm	124	128	105	109
Total number of cases	138	139	119	118

Maximum pulse rate in the first week

The pulse rate was counted every morning and evening throughout the admission The data recorded were analysed and the maximum pulse rate in the first week noted Tachycardia as a result of arrhythmias (atrial fibrillation flutter and ectopic rhythms) was excluded and will be discussed later

Table 26 shows the distribution of the maximum pulse rates in the first week The chi square homogeneity test was used and showed good agreement between the treated group and control group

TABLE 26

Maximum pulse rate in the first week

Pulse rate	Section A Treated	Section A Control	Section B Treated	Section B Control
50– 59	1	1	0	1
60– 69	7	5	6	4
70– 79	14	15	13	13
80– 89	34	41	28	31
90– 99	32	28	28	25
100–109	32	32	28	29
110–119	14	10	12	8
120–129	4	6	4	6
130–139	0	1	0	1
Total number of cases	138	139	119	118

The pulse rate in acute myocardial infarction is related to the immediate prognosis This has been shown by many authors including *Wright Marple and Beck* (1954) who give references to other investigations dealing with this subject In the present study a pulse rate of 100 per min or more was recorded in 99 patients (36 %) and one of 120 per min or more in 11 patients (4 %)

Blood pressure

It is generally recognised that acute myocardial infarction is often followed by a fall in blood pressure Lack of knowledge about the previous blood pressure in many of the patients (see p 65) made it impossible to obtain an exact figure for this fall in blood pressure The possibility of making a comparison with the blood pressures found later in the observation period was also considered to be of little value as after an infarct the blood pressure often remains low for a long time It would be difficult or impossible to be certain of stable values for such a comparison unless there was a very long observation period This was not possible in many of the cases who died early

On the other hand the lability of the blood pressure in the acute phase of the disease was considered to be related to the severity of the infarct and to the prognosis It was intended to obtain an impression of this lability for comparison of the treated group and control group by looking at the following data recorded during the first 8 days after admission in all the patients (1) Highest systolic blood pressure (2) Highest diastolic blood pressure (3) Difference between the

highest and lowest systolic pressures (4) Difference between the highest and lowest diastolic pressures

The distribution of these findings is shown in *Tables 27–30* On looking at these tables it will be noticed that the highest systolic pressure in the control group is on the whole lower than that in the treated group (Table 27) It is also clear that the difference between the highest and lowest systolic pressures is in many cases less in the control group than in the treated group (Table 29)

TABLE 27

Highest systolic blood pressure recorded during the first week

BP values	Section A Treated	Section A Control	Section B Treated	Section B Control
≦110	8	14	6	12
115–120	5	17	5	15
125–130	15	19	14	16
135–140	19	21	18	17
145–150	25	23	20	20
155–160	22	7	19	6
165–170	19	11	17	11
175–180	8	14	7	11
185–190	7	5	6	5
195–	10	8	7	5
Total number of cases	138	139	119	118

TABLE 28

Highest diastolic blood pressure recorded during the first week

BP value	Section A Treated	Section A Control	Section B Treated	Section B Control
≦ 70	6	8	4	6
75– 80	15	32	14	26
85– 90	41	38	34	33
95–100	39	30	35	25
105–110	21	18	18	16
115–120	9	8	8	7
125–	7	5	6	5
Total number of cases	138	139	119	118

Statistical analysis of these figures using the chi square homogeneity test had the following result There is no significant difference between the treated group and control group either for the distribution of the highest diastolic

TABLE 29

Difference between the highest and lowest systolic BP during the first week

Difference between BP values	Section A		Section B	
	Treated	Control	Treated	Control
≦ 5	5	13	5	11
10	9	16	9	14
15	10	18	10	18
20	17	10	14	7
25	8	14	6	8
30	22	14	17	11
35	8	6	6	6
40	7	8	5	7
45	5	9	5	9
50	10	14	9	11
55–65	27	6	25	6
70–	10	8	8	7
Total number of cases	138	136*	119	115*

In the control group the BP was only measured once in 3 patients

TABLE 30

Difference between the highest and lowest diastolic BP during the first week

Difference between BP values	Section A		Section B	
	Treated	Control	Treated	Control
0	5	8	5	6
5	14	13	13	12
10	27	32	19	27
15	19	15	16	13
20	24	30	22	26
25	11	10	11	9
30	12	14	10	9
35	5	6	3	5
≧40	21	8	20	8
Total number of cases	138	136*	119	115*

In the control group the BP was only measured once in 3 patients

pressures or for the difference between the highest and lowest diastolic pressures But there *is a significant difference* between the highest systolic pressures and in the difference between the highest and lowest systolic pressures The difference is most marked for the difference between the highest and lowest systolic pressures in section A Only in 3 out of 1000 cases can one expect a larger chi square value under the null hypothesis

The highest systolic blood pressures have an average value in section B of 152 46 mm Hg in the treated group and 144 28 mm Hg in the control group A Student s T test showed that there was also a significant difference between these average values It was found that $T = 2\ 43$ and Prob $(T > 2\ 43) = 1\ 5\ \%$ There is thus only 1 5 % probability for a larger chance variation

This pronounced significance is surprising especially as all the other comparisons made were in such good agreement The question is therefore does this significant difference depend on a real difference in blood pressures in patients in the treated and control groups or was there some systematic difference in taking the measurements in the two groups?

When the temperature charts were gone through to record and tabulate the values *one* striking difference was noticed between the treated group and control group namely *the number of measurements* taken While the number of measurements in the treated group was usually that planned and in many cases extra readings were taken the opposite was true in the control group In many cases only two measurements were taken and in 3 cases (see Tables 29 and 30) only one measurement was taken during the first week This difference is connected with the method used for allocation of patients to the treated and control groups As mentioned earlier (see p 46) most of the treated group was from Dept VIII and most of the control group from Dept VII while patients from Dept IX were allotted to both groups though most were in the control group It has been mentioned before that Dept VIII is more interested in cardiovascular disease than the other two departments (see p 46) It is therefore natural that measurement of blood pressure in this department has a more important place in the normal routine Further the author was only able to supervise the taking of blood pressures in Dept VIII where he worked

The fact that the blood pressure is so labile in the period investigated might together with the difference in how often the readings were taken easily account for the significant statistical difference between the treated and control groups The increased number of observations in the treated group will furnish a greater number of especially high and low values As the systolic pressure is much more labile than the diastolic one would expect the difference in number of measurements to affect these results most and even more the difference between the highest and lowest systolic pressure—and this is in fact what happened

Shock

The number and distribution of patients who showed signs of shock is shown in *Table 31* There is clearly no significant difference between the treated and control groups Serious life threatening shock was observed in 7 cases 4 in the treated and 3 in the control group In section B there were two cases in each group In all signs of shock were observed in 62 of the 277 cases in section A i e 22 %

TABLE 31

Signs of shock

	Section A Treated	Section A Control	Section B Treated	Section B Control
Shock	29	33	25	26
No shock	109	106	94	92
Total number of cases	138	139	119	118

Wright Marple and Beck (1954) observed shock (all grades from mild to severe) in 29 % of their cases As the patients in the present investigation had all survived the first month of the disease the incidence of shock is naturally lower

Position of the myocardial infarct on electrocardiography

The technique employed for electrocardiographic examination meant that accurate differences in the position of the infarct could not be ascertained The cases were divided into 5 groups (1) Cases with an infarct of predominating anterior character (anterior and antero lateral) (2) Cases with this characteristic and simultaneous signs of conduction disturbances (3) Cases with an infarct of predominating posterior wall character (posterior and postero lateral) (4) Cases with this characteristic and simultaneous signs of conduction disturbances (5) Cases with multiple infarcts or uncertain position of infarcts or diffuse changes

TABLE 32

Position of myocardial infarct on electrocardiography

Position of infarct	Section A Treated	Section A Control	Section B Treated	Section B Control
Anterior and antero lateral	68	61	65	57
Ant with conduction disturbances	7	8	5	6
Posterior and postero lateral	40	45	30	36
Post with conduction disturbances	7	8	6	6
Multiple or uncertain positions or diffuse changes	16	17	13	13
Total number of cases	138	139	119	118

The number and distribution of the cases in these 5 categories are shown in *Table 32* A chi square homogeneity test showed no significant difference between the treated and control groups

Arrhythmias and conduction disturbances

Arrhythmias and conduction disturbances are an important manifestation of the damage in the myocardium in acute coronary occlusion In most instances these disturbances are temporary or paroxysmal and disappear after minutes hours or days

Table 33 gives a general picture of the type number and distribution of the most important arrhythmias and conduction disturbances recorded during the acute phase of the infarct in this investigation

Extrasystoles (of all types) were observed in 44 patients (16 %) and were the most frequent form of arrhythmia A chi square goodness of fit test showed no significant difference between the treated group and control group

TABLE 33

Arrhythmias and conduction disturbances

Type of arrhythmia or conduction disturbance	Section A		Section B	
	Treated (138 cases)	Control (139 cases)	Treated (119 cases)	Control (118 cases)
Extrasystoles	19	25	15	23
Atrial fibrillation and flutter	10	12	10	9
Paroxysmal tachycardia (ectopic rhythm)	3	2	2	1
A-V block gr I	5	4	3	2
A-V block gr II	2	1	2	1
A-V block gr III	3	4	1	4
Bundle branch block	6	10	6	7

Atrial fibrillation and flutter were included in one group as these types of arrhythmia often occur in the same patient In section A fibrillation and/or flutter was observed in 22 patients (8 %)

Paroxysmal tachycardia was only seen in 5 patients Of these there were 1 in the treated group and 1 in the control group in section B with ventricular tachycardia

Different grades of *atrio ventricular conduction disturbances* were observed in 19 cases (7 %) If different grades of A-V block occurred in the same patient the case was only classified under the most severe grade

Bundle branch block right and left was shown in 16 cases (approx 6 %)

In the last categories of arrhythmia and conduction disturbance there was good agreement in the distribution between the treated and control groups

On the whole the incidences agree very well with those found by *Wright Marple and Beck* (1954)

Depts VIII and IX it was 3 12 % Together with other smaller technical dis agreements this difference in technique probably accounts for the marked statisti cal difference between the treated and control groups concerning the BSR values

Chambers (1946) points out that the BSR is useful in the diagnosis of myo cardial infarction but that the degree of elevation has no relation to the progno sis and *Treduay* (1947) has found a raised BSR just as common in fatal as in non fatal cases

In this investigation a BSR of 20 mm/hour or more was found in 94 % of the patients and one of 10 mm/hour or more in 97 %

Wright Marple and Beck (1954) found a definitely raised BSR in 95 % of their cases It seems now to be generally agreed that dicoumarol does not cause any rise in the BSR

Fasting blood sugar

All patients admitted to the three medical departments with myocardial infarction were meant to have a routine fasting blood sugar estimation the day after admission

TABLE 37

Fasting blood sugar

Blood sugar mg %	Section A Treated	Section A Control	Section B Treated	Section B Control
50– 59	0	1	0	1
60– 69	1	0	1	0
70– 79	5	2	5	2
80– 89	7	6	7	6
90– 99	11	11	11	8
100–109	25	22	20	21
110–119	22	29	20	23
120–129	19	21	15	18
130–139	10	9	8	8
140–149	10	8	9	7
150–159	7	5	6	5
160–169	2	4	1	3
170–179	1	0	1	0
180–189	1	0	1	0
Diabetes	7	5	5	3
Not investigated	10	16	9	13
Total number of cases	138	139	119	118

Table 37 shows the distribution of the blood sugar values The table shows that this investigation was not carried out in 26 patients in section A and that 12

patients had diabetes In the remaining 239 cases a fasting blood sugar of 130 mg % or more was found in 57 (24 %) This incidence is certainly lower than would be found if the estimation was carried out during the first 24 hours after the acute attack in more direct relation to the stress *Eckerstrom* (1951) found a fasting blood sugar of 130 mg % or more in 111 out of 162 cases (69 %)

A chi square homogeneity test was used on the blood sugar values and showed no significant difference between the treated and control groups

Serum cholesterol xanthelasma xanthomatous nodules

Table 38 shows the distribution of the values for total serum cholesterol estimated by *Kingsley and Schaffert's* method The chi square homogeneity test showed no significant difference between the treated group and control group

TABLE 38

Total serum cholesterol

Cholesterol value mg %	Section A		Section B	
	Treated	Control	Treated	Control
125–149	3	4	2	3
150–174	6	7	4	5
175–199	5	11	5	10
200–224	21	12	18	10
225–249	18	30	17	25
250–274	23	22	18	20
275–299	27	19	26	19
300–324	10	9	10	7
325–349	11	9	9	7
350–374	5	4	5	4
375–399	1	3	1	2
400–424	2	2	1	2
425–449	1	1	1	0
450–474	2	2	2	1
475–499	0	0	0	0
500–	1	1	0	1
Not investigated	2	3	0	2
Total number of cases	138	139	119	118

A total serum cholesterol of 300 mg % or more was found in 64 cases (23 %) and one of 400 mg % or more in 12 cases (4 %) *Wright Marple and Beck* (1954) found a serum cholesterol of 300 mg % or more in 15 % and 400 mg % or more in 3 % of their cases In their investigation several different methods were used for the cholesterol estimation

Table 39 shows the number and distribution of cases in which xanthelasma was shown on the eye lids the number with xanthomatous nodules and the number with signs and past history evidence of definite familial xanthomatosis (Muller s disease) *There is obviously no significant difference* between the treated and control groups

The table shows that there were very few patients with these clinical manifestations Some of these cases did not have hypercholesterolaemia The two patients with familial xanthomatosis did not have very high serum cholesterol values the averages being 277 and 336 mg %

TABLE 39

Xanthelasma xanthomatous nodules familial xanthomatosis

	Section A		Section B	
	Treated (138 cases)	Control (139 cases)	Treated (119 cases)	Control (118 cases)
Xanthelasma	6	4	5	3
Xanthomatous nodules	3	2	2	2
Familial xanthomatosis	1	1	1	1

Cardiac volume estimated radiologically

Although at post mortems an increase in the weight of the heart is often found in cases of coronary disease the significance of the size of the heart has been given relatively little attention in clinical studies of the prognosis *Palmer* (1937) found that clinical heart failure after survival from an acute myocardial infarct only occurred in cases with enlarged hearts and that the incidence of recurrent infarction dyspnoea and reduced activity was greatest in this group He found oddly enough that the size of the heart was of little significance for the length of survival time This was also found by *Master and Jaffe* (1951) The present author believes however that the size of the heart is of great prognostic significance and should be given more attention in studies of the prognosis in coronary disease than has previously been the case

Radiological measurement of the cardiac volume is undoubtedly superior to clinical examination for measuring the size of the heart Although there are many sources of error it also provides better opportunities for comparing both the size of the hearts of two patients and that of the same patient at different times

In this investigation the patients were X rayed about 4 weeks after the acute attack Of the cases in which the examination was not successful or had not been *done by the end of the first month (see* Tables 40 *and* 41) *all the cases included* in section B were X rayed in the next few months The results of these delayed examinations are not included in the comparison made here

TABLE 40

The cardiac volume estimated radiologically in men about 1 month after the acute myocardial infarct

Cardiac volume ml per square metre body surface area	Section A Treated	Section A Control	Section B Treated	Section B Control
300–340	4	5	4	3
350–390	12	14	10	14
400–440	31	20	31	20
450–490	19	21	17	20
500–540	16	21	14	17
550–590	5	9	5	7
600–640	1	3	1	3
650–690	1	3	1	3
700–740	1	1	1	1
Not investigated*	7	7	4	5
Total number of cases	97	103	88	93

See footnote under Table 41

TABLE 41

The cardiac volume estimated radiologically in women about 1 month after the acute myocardial infarct

Cardiac volume ml per square metre body surface area	Section A Treated	Section A Control	Section B Treated	Section B Control
300–340	3	1	3	1
350–390	14	10	11	8
400–440	6	9	5	8
450–490	5	5	4	3
500–540	2	3	2	2
550–590	2	3	1	0
600–640	0	0	0	0
650–690	0	1	0	1
Not investigated*	9	4	5	2
Total number of cases	41	36	31	25

* The cardiac volume was not measured during the first month in these cases partly because of technical difficulties with the X rays i e pleural effusion or thoracic deformities preventing measurement and volume calculation and partly because X rays could not be taken or it was forgotten to take them before discharge

Tables 40 and 41 show the distribution of the cardiac volumes (calculated per square metre body surface area) in men and women in this investigation The

results for men and women in section B were tested with the chi square homogeneity test and showed no significant difference between the distribution of the cardiac volumes in the treated and control groups The average cardiac volume *in men* was 450 83 ml in the treated group and 468 21 in the control group and *in women* 401 54 in the treated group and 424 78 in the control group The differences were tested with Student s T test and showed no significant difference between the treated and control groups for men or women There is thus no significant deviation in the distribution of the cardiac volumes even though the average volume is larger in the control group in both sexes

Using the same method of radiological examination and volume calculation *Amundsen* (1956) states that the cardiac volume in *men* is normally ≦ 490 ml/square metre body surface area definitely increased volume ≧ 550 ml Volumes from 500 to 540 ml represent the uncertain border line between normal and pathological values In *women* the corresponding figures are ≦ 440 ≧ 500 and 450–490 ml/square metre body surface area Of the 221 cases investigated in section B a definitely pathologically enlarged heart was shown in 28 cases (13 %) 11 in the treated and 17 in the control group There is thus a slightly larger number of cases with enlarged hearts in the control group than in the treated group Although the difference is not statistically significant it should be noted that the control group is less favourably situated

Summary and conclusion

As mentioned in Chapter IV when collecting the material for this investigation it was not possible to assign the patients to the treated and control groups by drawing lots Further some of the patients originally included (section A) had to be excluded from the investigation for different reasons (see Chapter V) In this way section B was formed and provided the basis for the investigation

In this chapter a detailed analysis and statistical comparison of the comparability of the treated and control groups at the beginning of the investigation is given This comparison was made both for the original material (section A) and for the material which formed the basis of the investigation (section B) as it was thought important to see whether the exclusion of patients had biased the comparability

The statistical comparison was made for many different criteria Roughly speaking these criteria fall into 3 main groups

(I) General characteristics Age sex race geographical location social standing height and weight

(II) Conditions in the past history thought to have significance for the prognosis Previous angina pectoris myocardial infarction hypertension heart failure valvular disease cerebral vascular accidents obliterating arterial disease diabetes mellitu

(III) Course of the recorded infarct Prodromal symptoms attack at rest or on exertion interval between acute attack and admission pain vomiting dyspnoea heart failure pericardial friction rub gallop rhythm maximum pulse rate during first week blood pressure shock position of infarct on electrocardiography arrhythmias and conduction disturbances maximum temperature during first week white cell count BSR fasting blood sugar serum cholesterol and cardiac volume estimated radiologically

With the level of statistical significance chosen (5 %) there were only 2 of all the conditions investigated where there was a significant difference in distribution between the treated group and control group namely the systolic blood pressure during the first week and the highest BSR recorded during the admission In both instances higher and more scattered values were found in the treated than in the control group The difference shown in the blood pressures is not a true difference but may be explained by differences in the number of measurements taken For the BSR a systematic error in the technique (difference in citrate concentration) was probably the cause of the disagreement

The number of patients who had had a previous myocardial infarct was larger in the treated group than in the control group 16 as against 11 cases (section B) The difference thus favours the control group although it was not statistically significant On the other hand there were more patients with enlarged hearts in the control group than in the treated group 17 as against 11 cases (section B) and the average cardiac volume was also a little larger in the control than in the treated group Although this difference was also not significant it favours the treated group and perhaps roughly speaking it cancels the effect of the differences in number of patients with previous infarcts

On the whole the statistical comparison of the patients in the treated and control groups provides a good basis for stating that *the patients were allotted by chance to the two groups* The many different characteristics compared in the investigation provide good support for this assumption although some of them are inter dependent

CHAPTER VII

Treatment of the acute infarct during the first month

This investigation was planned so that the management of the patients in both the treated and control groups should be as similar as possible from the time they were admitted into hospital until the beginning of the observation period one month later The question of the use of anticoagulants during this period has been referred to earlier It was not considered necessary to plan other treatment in more detail The same general principles in the treatment of the acute phase of the infarction were followed in each of the three departments to which the cases were admitted There is therefore no reason to believe that the results are biased by the treatment in the acute phase

The management of the patients in the treated and control groups in the first month will now be gone into in more detail so that it can be seen how far one is justified in considering the treatment of the groups comparable

The medical care nursing and general care of the patients will first be described partly to assess the degree to which the cases are comparable and partly in order to point out the conditions in a Norwegian Public Hospital which differ in several respects from those in hospitals in many other countries

Medical care

As mentioned earlier the cases in this investigation are from three equally large medical departments each with about 150 beds and each with independent medical administration In each department there are 10 physicians who have permanent full time appointments and who are paid by the hospital

There is a Chief (Professor) who is responsible for the medical administration and decides the general principles to be followed The second in command is the Sub chief (Lecturer) he helps the Chief to supervise the management of each individual case In each department there is also one Reserve Physician and three Assistant Physicians who hold appointments which are renewable 4 yearly and are fully qualified specialists in medicine Finally in each department there are four fully qualified doctors Candidates who have usually specialised to a certain extent after taking their degree examinations but who are not fully qualified specialists

Each department is divided into 4 wards each with 30–40 patients These are supervised daily by the Reserve or one of the Assistant Physicians with the help

of one of the Candidates but are under the supervision of the Chief and Sub chief

Each of the 4 Candidates together with the Reserve Physician or one of the Assistant Physicians have alternating afternoons and evenings on call The Candidate on duty examines all the patients on admission and dictates the medical history New admissions are always examined by the Reserve or Assistant Physician on duty and he orders the special tests which he considers necessary and starts the medical treatment if necessary in consultation with the Chief and/or Sub chief During the night new admissions are examined by the Candidate on call who lives in hospital In all acute or difficult cases he telephones the Reserve or Assistant Physician on call and either asks his advice or calls him in

Throughout the rest of the patient s illness the history is kept up to date by the Reserve or Assistant Physician in whose charge the patient is and he supervises the investigation and daily treatment The medical findings and treatment are checked regularly by the Chief and Sub chief who make certain that the case history gives a correct picture of the situation All acute or difficult cases are more closely supervised and discussed so that each individual case can benefit from the combined experience of the members of the medical staff

Nursing

Each department has a permanent staff of fully qualified nurses who are employed and paid by the hospital A fairly large number of student nurses also take part in nursing the patients These attend the hospital s training school for nurses and they are instructed in their work by permanently employed sister tutors The nurses and student nurses work in each department is supervised by a sister The daily nursing in each of the four wards is supervised by an experienced nurse who makes sure that every patient gets the attention and comfort that the individual case needs She is responsible for the investigations being carried out on the patient and for the giving of the prescribed drugs and treatment at the correct times

The management of the nursing and the number of fully qualified nurses and student nurses is also the same in all three departments

General care

The general care of the patients is uniform throughout the hospital There is only one type of care given— better care or private care does not exist

Practically everyone in Norway belongs to the Personal and Employees Benefit Scheme and this therefore pays for the whole stay in hospital inclusive of special investigations and all drugs regardless of expense so that the patient himself has no financial expenditure either to the hospital or to the doctors The very few

patients who do not belong to the Benefit Scheme pay fees to the hospital themselves The fee per day is fixed and even if the case demands a large number of extra examinations by specialists or expensive drugs this will not mean extra expenses for the patient

The three medical departments under consideration are as mentioned above on separate floors in the same block and the rooms that make up each department are identical The number of beds in the rooms varies between 2 and 7 apart from one room in each department which takes 22 male patients As far as possible the worst cases are in the smallest rooms

The patients cannot hire private nurses In cases where nursing is particularly difficult or takes a lot of time so that the staff of the ward cannot cope with the nursing during their working hours the sister will arrange for a sufficient number of extra nurses These nurses are also employed and paid by the hospital and they do not represent any increased expenses for the patient

Medical and dietetic treatment

A detailed analysis of the treatment of the acute infarct in order to assess the comparability of the treated and control groups seemed superfluous in connection with the present problem We will content ourselves with a description and discussion of facts of essential importance

Use of digitalis

The use of digitalis is of interest as it can be regarded as an indication of clinical or impending heart failure *Table 42* shows the number of patients who received digitalis there is no significant difference between the treated and control groups

TABLE 42

Type of treatment	Section A Treated (138 cases)	Section A Control (133 cases)	Section B Treated (113 cases)	Section B Control (118 cases)
Digitalis	16	17	12	13
Salt restriction	16	17	12	12
Calorie restriction	19	17	18	15
Oxygen	23	13	18	7
Transfusion (Plasma blood etc for shock)	8	1	6	1

Salt restriction

A low salt diet is of the same significance as the use of digitalis *Table 42* shows the number of patients in each group who received this form of treatment It is evident that there is good agreement with the figures for digitalis and that there is no significant difference between the two groups

Restriction of calories

A comparison has already been made of the weights of the patients in the treated and control groups (See page 63) The use of a low calorie diet illustrates the question of obesity from another angle The number of patients treated in this way is shown in *Table 42* There is no significant difference between the two groups

Use of oxygen

Oxygen was only occasionally used in the treatment of acute myocardial infarction in the three medical departments to which these patients were admitted

It was usually given through oxygen glasses which had two short tubes leading into the nostrils The number of patients who received oxygen is shown in *Table 42* It is evident that about twice as many patients received oxygen in the treated as in the control group These figures must however be accepted with reservation When oxygen was used it was usually a temporary measure in the management of severe cases with dyspnoea or signs of pulmonary oedema immediately after admission often before the case history was taken It is reckoned that oxygen was given to several patients without the fact being noted in the case history and therefore not recorded here

Treatment of shock by transfusion of blood or related substances

Treatment of shock by transfusion of blood plasma or serum was only given to a total of 9 patients i e 8 in the treated group and only 1 in the control group (Table 42) This difference is not fortuitous This form of treatment was introduced into Dept VIII while this investigation was going on and it was found to be beneficial in some cases In Depts VII and IX this treatment was accepted with reserve as it can represent an extra load on the heart with danger of pulmonary oedema In the control group transfusion was therefore only given in one case in which the Reserve Physician from Dept VIII was consulted

In one case in the treated group (in section B) who developed very severe and protracted shock 1000 ml serum + 500 ml blood were given in two hours and this was considered to have saved the patient s life In the other 8 cases it is doubtful whether this treatment influenced the outcome

Use of dicoumarol

Dicoumarol was the oral anticoagulant used and it was given to all the patients in both groups The drug was started immediately in all cases where myocardial infarction was suspected or when there were definite clinical signs of infarction Blood for estimation of the PP value was taken before the first dose of dicoumarol (except in a few cases admitted at night) All cases were given a fixed initial dose i e 250 mg and 125 mg next morning if the first dose was given before 2 pm after 2 pm a 200 mg initial dose was followed by 100 mg the next morning

Throughout the rest of the stay in hospital the PP value was estimated regularly 3 times a week (Monday Wednesday and Friday) with extra estimations if necessary In all the cases an accurate graph on millimetre paper was made showing the PP values and the daily doses of dicoumarol The dose of dicoumarol was based on the patient s tolerance as shown by the graph of the PP values The drug was given each morning in a maintainance dose with the object of keeping the PP value constant in the region of the therapeutic optimal i e between 10 and 30 % For more details on the technique of dose regulation the reader is referred to an earlier publication by the author *(Bjerl elund 1953)*

The regulation of the dose of dicoumarol was carried out by the author in all the three departments throughout the period of this investigation This was done partly to insure uniform anticoagulant treatment and partly as in this way the author got to know about all patients with suspected or definite myocardial infarction soon after they were admitted

It was made certain that the treatment was as effective as possible and that exactly the same method of dosage and control was used in all the cases There is no reason to suppose that there was any difference in the effect of dicoumarol treatment between the treated and control groups A detailed analysis of the PP values during the treatment of the acute infarction is not considered necessary in relation to the present problem Indirectly the effect of the anticoagulant treatment will appear below during the discussion of the haemorrhagic and thromboembolic complications during the first month in both groups of patients

Duration of treatment with dicoumarol in the control group

As mentioned earlier the patients in the control group according to plan should have received dicoumarol during the acute infarction for a maximum of 1 month (30 days) In practice it was difficult to be completely accurate *Table 43* shows the number of days for which dicoumarol was given in the control group including both section A and section B In section B the table shows that dicoumarol was stopped within 30 days in 101 out of 118 cases Of the 14 cases

TABLE 43

Duration of treatment with dicoumarol in the control group

Duration of treatment	Section A	Section B
16–20 days	5	3
21–25 –	11	8
26–30 –	103	90
31–35 –	16	14
36–50 –	4	3
Total number of cases	139	118

where the table shows that dicoumarol was stopped after 31–35 days there were 12 who received dicoumarol for a maximum of 32 days Therefore the drug was stopped within 32 days in 113 out of the total 118 patients Of the 5 patients who were treated for a slightly longer time there were 3 in whom the doctor in charge of their daily treatment considered that more protracted treatment was advisable in view of their condition There was however no clinical evidence of thrombo embolic complications in these cases In the other 2 cases the treatment was continued for slightly longer by mistake The figures for section A are shown in the table and show no significant differences from section B

Use of heparin

Initial use of heparin in order to obtain a quicker anticoagulant effect was very seldom used in the 3 medical departments during this investigation It was therefore not considered necessary to issue special instructions for its use in connection with the investigation It was left to the individual physician treating the case to decide whether or not to use it The author therefore had nothing to do with this aspect of the treatment

Heparin was never given for more than 3 days to any of the cases In most cases it was only given for 1–2 days There were only 35 cases who received heparin out of the total 277 cases including the patients who only received one injection Of these 24 were in the treated group and only 11 in the control group This difference which is not fortuitous is completely explained by the fact that in this respect the treatment varied from department to department None of the 91 patients in Dept VII received heparin Of 119 patients from Dept VIII there were 18 who got heparin (all in treated group) and of 67 patients from Dept IX 17 got heparin of whom 11 were in the control group and 6 in the treated group Of the patients in section A who received heparin there were 7 who were excluded 5 in the treated group and 2 in the control group In section B there were therefore 19 and 9 patients in the two groups

This difference in the use of heparin certainly does not affect the comparability of the two groups in relation to the problem of this investigation This will also be apparent when the incidence of thromboembolic complications in the acute phase in the two groups is compared below

Complications during treatment of the acute infarct in the first month

It has already been mentioned that serious complications in some patients in section A excluded these cases from further observation To avoid repetition only the occurrence of complications in section B will be mentioned

Haemorrhagic complications

Serious or life threatening haemorrhage was not observed as a result of the use of anticoagulants during the first month in hospital Moderate haemorrhages occurred in 4 patients in the treated and 5 in the control group

Treated group

Epistaxis—1 case PP value 20 % (Anterior plugging and later electrocautery of a dilated vessel which was the source of haemorrhage)

Macroscopic haematuria—1 case PP value 5 %

Chemical haematuria (Positive benzidine reaction)–1 case PP value 5 %

Blood on defaecation fresh macroscopic—1 case PP value 6–7 %

Control group

Macroscopic haematuria and haemoptysis—1 case PP value 3–4 %

Melaena—moderate for 2 days—1 case Hb 100–80 % PP value 5 %

Bleeding haemorrhoids moderate 1 case PP value 15 %

Bleeding haemorrhoids considerable—1 case PP value 8 % A blood transfusion 1 litre was given When the haemorrhage occurred this patient had had dicoumarol for 3 weeks it was therefore permanently discontinued

In the three last cases in the treated group and the two first in the control group in which the PP value was very low (approx 5 %) 50 mg water soluble vit K (menadion) was given i v

Apart from the last case dicoumarol was not completely stopped it was sufficient to withhold the drug for a day or two until the PP value was no longer near the dangerous level

It is obvious that the occurrence of haemorrhagic complications was equally distributed between the two groups both as regards the number of cases and the severity of the haemorrhage and that reasons other than the use of anticoagulants were contributory causes in some cases

Thromboembolic complications

Definite signs of thromboembolic phenomena occurred in 3 patients One patient in the *treated group* developed cerebral embolism with right sided hemiparesis and aphasia on the 3rd day after admission Her PP value on the day before this episode was down to 37 % 2 days later it was 8 % She made a good recovery from her hemiparesis and she was not excluded from the investigation

Two patients in the *control group* developed signs of pulmonary embolism In one of these the symptoms were already present on admission In the other the symptoms appeared during the 2nd week of treatment at the same time as a transitory rise in PP value to 44 %

Pulmonary and/or pleural complications of possible but not certain thrombo embolic pathogenesis occurred in 5 patients 2 in the treated and 3 in the control

group Two patients in the former and 1 patient in the latter group showed on admission before treatment was started clinical and radiological signs of basal consolidation in the left lung None of these patients had haemoptysis and it was not possible with certainty to make a differential diagnosis between pulmonary embolism and pneumonia One of these patients (in the treated group) developed a moderate pleural effusion on the same side during the 3rd week One patient in the control group developed right pleuritic pain in the 3rd week and pulmonary embolism was suspected X ray showed bilateral pleural effusions which were haemorrhagic on puncture and which persisted for many weeks In this case the PP value remained in the therapeutic optimal region varying from 19 to 11 % during the 8 days before the effusions occurred and the 14 days after In another patient in the control group X ray at the end of the 4th week showed a moderate effusion in the left pleural cavity The patient was symptom free In this patient the treatment had been completely adequate (PP value 10–20 %) in the 3 weeks preceeding and at the time the complication occurred

(One patient in the treated and one in the control group developed signs of considerable bilateral pleural effusions Both these patients had severe heart failure and the appearance of the effusions was attributed to this In the patient in the treated group repeated tapping of the effusion was necessary)

These facts show that thromboembolic complications during the acute phase were very few and that the distribution was very similar in the two groups Of the definite thromboembolic episodes the pulmonary embolism in the control group might have been prevented if the dicoumarol dosages had been ideal The other two cases could not have been prevented by dicoumarol but if heparin had been used at the onset it might have been possible to prevent the case of cerebral embolism in the treated group The doubtful thromboembolic episodes were either present when the patient was admitted or they occurred when the treatment was completely adequate It is therefore improbable that these could have been prevented by treatment

Complications with no direct relationship to the heart or to anticoagulants

Complications during the acute phase apart from those already mentioned were few and of little clinical importance They will therefore only be mentioned briefly

In the *treated group* mild attacks of gout were observed in 2 cases peritendinitis humeroscapularis in 2 cases acute cystitis in 1 case and a tooth abscess with spontaneous perforation in 1 case One patient with syncope in relation to the acute attack before admission developed symptoms of mild concussion

In the *control group* a cold with herpes labialis and temporary recurrent laryngeal nerve paresis was observed in 1 case highly febrile Vincent s angina in 1 case acute vulvovaginitis in 1 case parotitis with abscess formation and spontaneous perforation in 1 case and seborrhoeic eczema in 1 case

Length of time in hospital

Table 44 shows the length of time in hospital for the recorded cases of acute infarct in the two groups It is evident that on the whole the patients in the control group were a little longer in hospital and that this difference occurred because quite a large number of patients in the treated group were discharged before the end of the first four weeks In section B this occurred with 25 patients in the treated and only 8 in the control group

TABLE 44

Length of time in hospital

Days in hospital	Section A		Section B	
	Treated	Control	Treated	Control
8–14	4	0	2	0
15–21	4	1	4	0
22–28	22	10	19	8
29–35	53	57	48	51
36–42	28	41	24	39
43–60	18	23	16	18
61–90	5	4	3	1
90–	4	3	3	1
Total number of cases	138	139	119	118

The difference in length of time in hospital between the two groups is not fortuitous It occurred as the physicians treating the patients in the control group wanted these to have full benefit from anticoagulants within the given period This is also shown in Table 43 page 92 The patients in this group had to remain in hospital until the treatment was stopped On the other hand the knowledge that the patients in the treated group would continue to receive anticoagulants after discharge from hospital meant that if the home conditions were good and the department short of beds these patients were discharged somewhat earlier

Table 44 shows that the number of cases whose condition necessitated a considerably longer stay in the ward was very evenly divided between the groups There were thus in section B 22 patients in the treated and 20 in the control group who had to be in hospital for over 6 weeks

As regards the duration of time in bed the patients in this investigation were all treated conservatively Neither mobilisation after only 2 weeks as advised by *Irwin and Burgess* (1950) nor armchair treatment as proposed by *Levine and Lown* (1951) were used Almost all the patients were kept in bed for about 4 weeks or slightly longer Only the mildest cases and those in whom the interval between

the acute attack and admission to hospital was relatively long were allow slightly earlier There was no fundamental difference in the amount of be in the different departments and a detailed analysis was not considered nec

Condition on discharge

In planning this investigation it was arranged that the case history state the condition of the patient on discharge with especial regard presence of angina pectoris or signs of heart failure This is shown in Ta The table shows that there is very good agreement between the treate control groups in this respect Three patients in the treated group and 4 control group died in the ward after more than 30 days in hospital for r that will be mentioned later These patients therefore do not appear in this

TABLE 45

Condition on discharge	[illegible] Treated ([illegible])	[illegible] Control ([illegible])	[illegible] Treated (119 cases)	[illegible]
Angina pectoris	19	19	17	
No angina pectoris	116	116	99	
Clinical heart failure	4	3	7	
No signs of heart failure	131	132	113	

Three cases in the treated group and 4 in the control group [illegible] in this table

Summary and conclusion

In this chapter it is shown that the conditions governing the medica nursing and general care which were at the disposition of all the patients investigation during the course of the acute infarct were uniform regard economic or social position There was no difference in this respect betwe 3 medical departments and therefore none between the treated and control p

An analysis of the treatment of the cardiac condition (not including antic lants) also showed the same conditions in both groups The only exceptions the use of oxygen and the treatment of shock with blood or related subs which were used in a few more patients in the treated than in the control (see p 91) On the whole only very few patients received such treatment a difference mentioned has hardly had any effect on the further comparati the groups

Use of dicoumarol in the first month was supervised and the doses pre by the author in exactly the same manner for all the patients in both g There is thus [illegible] that there was any difference as r

rence of both haemorrhagic and thromboembolic complications was practically evenly distributed between the two groups

Initial treatment with heparin which on the whole was very little used occurred slightly more often in the treated than in the control group for reasons mentioned on page 93

Non cardiac complications during the first month were of little clinical significance and were evenly distributed between the groups

The number of patients who on discharge had signs of angina pectoris or signs of heart failure even on slight exertion was also the same in both groups

It can therefore be stated that the patients in the treated and control groups in all important matters received similar treatment and the course of their disease was similar in the first month after admission There is thus no reason to suppose that the treatment in this period has influenced the comparability of the groups during the further course of the illness It must be assumed that they are comparable when considering the problem of this investigation

CHAPTER VIII

Observation and treatment in the ambulant phase
Length of observation

In the two previous chapters it has been shown that there is no certain statistical difference between the two groups either as regards the general characteristics past history symptoms and signs during the period of acute infarction or as regards treatment complications and course of the disease during the first month after admission Therefore as far as can be judged from the points analysed there is reason to believe that the two groups are comparable at the beginning of the observation period These cases should thus provide a good basis for the investigation of our problem

Management of the control group

After dicoumarol was stopped in the control group this aspect of treatment was fundamentally different in the two groups it is in fact the effects of this difference which were investigated

It is however obvious that the further course of the illness and the prognosis can be influenced by many other conditions some of which can be and some of which cannot be influenced by the doctor An important factor in this connection is the management of the cardiac condition apart from the use of anticoagulants

The use of anticoagulants provides in itself regular and frequent supervision of the patient It provides close contact and the possibility for thorough observation and treatment of the cardiac condition It is therefore clear that the patients in the control group should as far as possible be under similar observation and receive the same cardiac treatment apart from the use of anticoagulants

A routine cardiac clinic every 2–3 weeks would not have been practicable and was not considered necessary or appropriate But it was arranged that the patients in the control group should attend regular clinics including electrocardiography every 3–4 months

In all patients where acute infarction was suspected the case history laboratory findings and electrocardiograms were studied by the author while the patient was in hospital In all cases where the diagnosis was considered certain and the case therefore included in the investigation the patients were visited and examined In the patients in the control group especial weight was put on establishing personal contact with the patient The patients were told about the

cardiac clinic They also received a written statement in stencil form stating when and where they should attend This statement also included the author s telephone number so that the patient could let him know if it was not possible to attend the clinic and another time could be arranged The patient was also told that he could consult the author if special or unforeseen developments occurred during convalescence The form also mentioned that the cardiac clinic would not involve any expenses for the patient

It was soon apparent that this procedure worked very satisfactorily The patients in the control group attended regularly at the appointed date and time although the appointment had been made several months beforehand

At these clinics attention was regularly paid to the cardiac history with especial regard to the existence and degree of angina pectoris and symptoms of heart failure Further there was a routine clinical cardiac examination including measurement of blood pressure and electrocardiography

The author put especial weight on inquiring about and discussing other sides of the patient's life than the immediate cardiac symptoms e g conditions in the home conditions at work special personal problems etc This was done partly to acquire as much knowledge as possible of the patient s condition and partly to provide a better basis for the giving of advice instruction and consolation if necessary—an important aspect of all cardiac treatment Finally it was considered especially important and necessary to win the patient s confidence so that the control group could be kept intact and the investigation carried out according to plan

This last point was very topical While the investigation was going on the public got increasing knowledge of the significance of anticoagulants in the fight against thrombosis This happened partly through reports of medical meetings in the papers partly through popular medical radio talks and newspaper articles and last but not the least because an increasing number of patients with coronary disease were given anticoagulants continuously at clinics in different hospitals throughout the country The only thing to do in these circumstances was to try to give the patients in the control group as good and careful treatment as possible without anticoagulants They had the security and assurance that they were supervised by a doctor who was personally interested in giving them the best possible treatment and who was always willing to listen to their complaints

The question of the layman s increasing knowledge of medical questions and medical treatment is of special interest at the moment as it represents an important problem in all controlled clinical trials especially in an investigation like the present one which is of fairly long duration and where it is impossible to use placebos That the problem can have serious consequences and make the evaluation of the re ults difficult is seen amongst other places in the large American investigation on short term treatment with anticoagulants after acute myocardial infarction (See *Wright Marple and Beck* 1954 page 9)

The readiness of the author to be at the disposition of the patients in the control group in this way brought about very good contact with nearly all the patients in this group But it also entailed a great deal more work as the patients often asked for advice at times outside the normal clinics when they had a problem needing medical advice All the same this additional work also benefited the investigation firstly by providing better knowledge of the patients condition secondly as this was probably a very important reason for a nearly intact control group and thirdly because the author usually got to know immediately through either the patients or their relatives as soon as there was a serious change in their condition

In this way the author got the opportunity of giving cardiological treatment to the patients in the control group in the same way as in the treated group It was partly a question of providing physical and emotional relief by arranging for the patient to be off work for a time or help in transfer to lighter work or issuing medical certificates and partly treatment with drugs for angina pectoris institution of digitalis salt restriction and diuretics and also other cardiological treatment Altogether the 118 patients in section B in the control group reported 932 times during the observation period In addition to these several short consultations took place for the issue of prescriptions and medical certificates injections of mercurial diuretics etc which were not noted down

Management of the treated group

The diagnosis of acute myocardial infarct was confirmed in the patients in the treated group while they were in hospital in the same way as in the control group before the cases were included in the investigation Personal contact was then made with these patients in the same way Before discharge the continued administration of dicoumarol was explained to each patient the purpose and possible prophylactic value of the treatment was explained but at the same time the risk of haemorrhagic complications was mentioned The possible advantages of the treatment were presented with care and reservation partly because of lack of valid results and figures to assess the value of the therapy and partly because it was wanted to avoid giving the impression that there was any important difference between the treatment of the patients in the two groups There was only 1 patient who refused treatment and 1 who stopped treatment against the advice of the author after a couple of months Most patients in both groups seemed to feel that it was a definite safeguard to be kept under continued medical supervision and they were themselves anxious to attend

The regular thorough clinical and electrocardiographic supervision of the ambulant patients in the treated group was not carried out quite so frequently and regularly as it was in the control group The regular contact with the patients for estimation of the PP value every 1–3 weeks made it possible to keep up to

date with the condition of all these patients without such frequent thorough clinical examinations Electrocardiograms were taken regularly every 6 months and in the first 2–3 years of the observation period this was followed by clinical examination of the heart Later on uncomplicated cases were examined once a year Thorough clinical and electrocardiographic examinations were however carried out in all cases in which changes or deterioration developed Apart from the difference mentioned here which was partly a result of pressure of work the treatment of the cardiac condition both as regards the drugs used and the advice and psychotherapy given was the same in the treated and control groups

Recording and filing the data

After the patients had been discharged from hospital the author went through their case histories once more All the data of significance as regards past history symptoms and signs in hospital laboratory findings and complications were in each individual patient transferred to a card for filing especially made for use in this investigation Later observations at the clinics were recorded each time on this card as were notes of subsequent admissions to hospital

The hospital case history was stamped by the author asking that he should be told at once in case of re admission

When going through the case histories a portion of the most recent electro cardiogram taken in hospital was filed for comparison with later electrocardio grams at the clinic All the electrocardiograms were kept in a separate file A file was also made for all the graphs of PP values and the doses of dicoumarol used during the investigation

There was thus a file containing all the data in connection with the patients which was always kept up to date and which the author had available at every clinic throughout the observation period

Management of treatment with dicoumarol

Before being discharged from hospital the patients in the treated group were familiarized with the most important forms of haemorrhage which might occur It was stressed that immediately a haemorrhage occurred they must stop taking dicoumarol at once and contact the author They were all issued with a stenciled form which drew attention to the fact that they were receiving dicoumarol con tinuously after having had a myocardial infarct and that no surgical inter ference tooth extraction etc must be undertaken without consulting the author This form which was especially aimed at providing other doctors whom the patients might have to visit in an emergency with information also contained the author s official and private telephone numbers In this way everything was prepared so that if complications occurred the author got to know as quickly as possible and was able to intervene if necessary On the form it was also stated

that if admission to either a medical or surgical department was indicated admission to Ullevål Hospital either to Dept VIII or to a surgical department could be arranged In this way it was possible for the author to take part in the treatment if the patient was admitted to hospital and to prevent unnecessary breaks in the use of anticoagulants

The dose regulation of dicoumarol while the patients were ambulant was carried out by the author alone for the patients in this investigation This meant amongst other things that throughout the 6 years that the investigation lasted the author was not able to have more than 14 days holiday at a time The dose regulation was based on the PP values estimated by Owren s method which has previously been discussed in detail (See pages 27–29 and 49–52) During the first 2–6 weeks after discharge the PP values were estimated weekly in most patients In the following 2–3 years they were estimated regularly once a fortnight Later the interval between estimations was lengthened to 3 weeks in all the patients who had a stable PP graph on an almost constant dose of dicoumarol In some such cases the interval was prolonged to 4 weeks during the patient s summer holidays

A daily maintainance dose of dicoumarol was given with the object of keeping the PP value in the region of the therapeutic optimal which is considered to be between 10 % and 30 % (In a couple of cases only who had haemorrhagic complications or clinical hypertension the value was kept at a little higher level from 20–40 %)

This method of dose regulation of dicoumarol was originally introduced into Norway by Owren It has previously been described in detail by the author (*Bjerkelund* 1953) but a few of the chief points which are of especial interest in long term use in ambulant patients will be mentioned briefly

It is an advantage to be able to start treatment while the patient is in hospital so that the correct maintainance dose can be found before discharge This was possible in all the patients in this investigation

In all the patients an accurate graph of the PP values and doses of dicoumarol was made covering the whole period of treatment The value of such a graph cannot be overstressed The graph gives a visual impression of whether the doses given previously are correct too large or too small With increasing experience the graph is also valuable in assessing how far away the doses used are from the ideal doses Adjustment of maintainance doses in ambulant patients at relatively long intervals needs far more experience than dose regulation in hospital It can only be learnt by trial and error The long interval between each estimation of PP values makes it important to be very careful It is seldom necessary to make large alterations in the doses but a little adjustment is necessary even if the PP value has only changed 5–10 % in a couple of weeks An increase or reduction of the dose by 10–30 mg in the next fortnight is often sufficient in such cases i e an alteration corresponding to only 1–2 mg per day

In case of large deviations it is most logical and practical to make the main adjustment on the actual day of the clinic or in the next couple of days so that a continued rising or falling of the PP graph is counteracted as quickly as possible and the ideal level is re attained Afterwards the dose to be used in the next fortnight is corrected so that the PP graph is kept constant at the ideal level

It is of greatest importance to make certain that the patient really is taking the dose prescribed Even the most intelligent patient can be forgetful The necessity for taking the exact number of tablets every day must be impressed on the patients and if necessary repeated at intervals The author has made it a rule to let the patients have a written dose schedule where the dose for each day between the 2 clinics is given After having taken each day s dose the patient crosses it off the schedule If he then forgets to take the dose one day it will appear on the schedule and be brought to both the patient s and the doctor s notice Unfortunate consequences can thus be avoided and the patient s reliability and co operation stimulated

The dose schedule for each period was always given directly to the patient by the author throughout this investigation In most cases the schedule was written in the presence of the patient in the author s office as soon as the result of the PP value was available In some cases the dose was arranged over the telephone but it was always made certain that in such cases the patient was able to note the dose down so that it could be included in his schedule This is very important as the size of the tablets (20 mg dicoumarol) often makes it impossible to distribute the weekly dose as a constant daily maintainance dose so that the dose usually varies a little on different days

The daily maintainance dose necessary to keep the PP value in the region of the therapeutic optimal was in this investigation an average of about 60 mg varying between a maximum of 140 mg and a minimum of 17 mg per day

Experience has shown that it is difficult to keep to a stable maintainance dose and an even PP graph in patients with heart failure The reason for this is probably that variation in the degree of congestion in the liver causes changes in the synthesis of prothrombin and proconvertin with subsequent fluctuations in the tolerance to dicoumarol

That heart failure really does cause a fall in PP value has previously been shown by *Bjerkelund and Cleditsch* (1953)

Acute febrile diseases such as acute tonsilitis febrile catarrh or pneumonia not uncommonly cause a decreased tolerance to dicoumarol The reason for this is probably partly poor general condition but also often because patients are treated with antibiotics which alter the intestinal flora and thus the production of vitamin K and the synthesis of prothrombin and proconvertin in the liver

Similar alterations in the tolerance can be seen in acute gastrointestinal disturbances where both decreased absorption of dicoumarol and changes in intestinal flora may be contributory causes

Large excesses of alcohol can also sometimes cause unforeseen fluctuations which may well sometimes be due to the fact that in such conditions the patient is less vigilant in taking his dose of dicoumarol

In all intercurrent diseases one should therefore pay careful attention to the dose regulation There is risk that if the patient is in bed at home he will not be able to attend the clinic In such cases contact was made as soon as possible with the patient and if the disease was not of short duration blood was taken at a domiciliary visit

All estimations of the PP values while the patients were ambulant were carried out in the clinical laboratory of Dept VIII Ullevål Hospital The estimations were always done by technicians who were thoroughly trained to carry out the estimation and who were supervised by the author To rationalize this work and to save time the control blood tests were as fas as possible taken one afternoon a week Two trained technicians could then take blood and estimate the PP values for 50–60 patients in 3–4 hours

Length of observation

Before going over to study the results of the observation and out patient treatment a short account of the length of the observation time is of interest The patients in the treated and control groups were collected over exactly the same period and the observation time should therefore be comparable for the two groups But it is interesting to know for certain whether this holds good

As mentioned earlier all the patients in both groups received the same treatment in the first month (30 days) after admission to hospital with acute infarction The observation time with regard to the question of the prophylactic value of continued use of dicoumarol in the ambulant stage must therefore be reckoned as starting from and inclusive of the 31st day after admission From then on *all* the patients in section B were observed either till death or for a period varying between 31 and 68 months reckoned with regard to the end of the observation time i e 1st February 1956 More detailed data on the length of the observation time are shown in *Table 46*

It is shown in this table that a larger number of patients in the control group than in the treated group died during the observation period i e 42 and 24 patients respectively This fact influenced the total sum of the observation times which is 5 020 months in the treated group and 4 326 months in the control group In other words the patients in the treated group as a whole were observed during life for *694 months* longer than the patients in the control group The average observation time per patient is also longest in the treated group i e 42 2 months as against 36 7 months in the control group

If the observation time lost in each group on account of death is calculated reckoning from the death of the patient to the end of the observation time on the

TABLE 16

Observation time

Observation time in months	Treated	Control
0– 1	3 (3)	8 (8)
2– 3	2 (2)	2 (2)
4– 6	0	4 (4)
7–12	3 (3)	5 (5)
13–18	2 (2)	3 (3)
19–24	4 (4)	4 (4)
25–30	2 (2)	4 (4)
31–36	15 (6)	12 (3)
37–42	15	28 (5)
43–48	26 (1)	13 (2)
49–54	23 (1)	17
55–60	15	9 (1)
61–66	8	8 (1)
66–	1	1
Total number of cases	119 (24)	118 (42)

The numbers in brackets refer to the number of patients who died in each period of the observation time

1st February 1956 it is found to be 1316 months for the 42 patients who died in the control group as against 675 for the corresponding 24 in the treated group The difference is thus *641 months* This is in good agreement with the difference mentioned above between the actual observation periods in the treated and control groups (694 mths) minus the observation time for the one supernumerary patient in the treated group If we reckon this extra observation time as 48 months which is the average observation time for the patients in the treated group who are still alive we get 694 — 48 = *646 months* We can therefore conclude that the observation time in the treated and control groups are completely comparable and we therefore need to make no adjustments on account of this in the rest of this paper

Summary and conclusion

In this chapter the general lines followed and the treatment throughout the observation period of ambulant patients have been reported on It has been shown that all the patients in both groups have been under regular cardiological supervision by the author It is also shown that efforts have been made to give the control group as thorough cardiological supervision apart from the use of

dicoumarol as the patients in the treated group Possible differences in the prognosis during the observation period might therefore be the result of treatment with dicoumarol

The recording and filing of observed data is also mentioned Further attention has been drawn to the general lines followed during this investigation for the regulation of the dosage of dicoumarol and some facts of general interest in this connection have been mentioned Finally it has been shown that the observation time in the treated and control groups are completely comparable and that the collection of the material for the two groups has taken place over exactly the same period

CHAPTER IX

Intensity of the anticoagulant therapy as judged by the PP values recorded during the observation time

The primary object when a patient is given an anticoagulant is to reduce the coagulability of the blood thus as shown by experience reducing the danger of intra vascular coagulation and thrombosis *Wright Marple and Beck* (1954) have shown that the incidence of thromboembolic complications is related to the intensity of the anticoagulant therapy They found that in short term treatment the incidence of thromboembolic episodes was approximately twice as large when the prothrombin times for whole plasma were less than 25 seconds (over 23 % prothrombin activity) as when they were prolonged over this value On the other hand it was not until the prothrombin times were prolonged beyond 40 seconds (under 10 % prothrombin activity) that a significant increase in the incidence of haemorrhages was observed

Most workers who have published articles on the use of oral anticoagulants in ambulant patients give an accurate account of the method employed for prothrombin estimation of which anticoagulants have been used of the interval between estimations and of what is considered to be the optimal therapeutic region But it is only in exceptional cases that they mention to what degree it has been possible to maintain a stable and effective reduction of the prothrombin value

This state of affairs is regrettable as knowledge of this aspect of the treatment is necessary in fact of vital importance when assessing the effect of the treatment Many authors state that amongst the thromboembolic episodes during treatment so and so many occurred while the prothrombin value was not in the therapeutic region This tells us however nothing about the efficacy of the prophylaxis unless we are told at the same time the proportion of the total period of treatment that this was the case

There are probably several reasons for the scarcity of information about the results of the blood tests during treatment with dicoumarol One of the reasons is certainly the lack of uniformity both as regards methods and nomenclature The many different methods and modifications of methods which are in use have caused much confusion In addition to this the results are expressed in various ways prothrombin time prothrombin index prothrombin index per cent and "prothrombin value in per cent of the normal This last expression is in the

opinion of the author much the best as it immediately makes a comparison with other results possible There is no constant relationship between prothrombin time in seconds (or prothrombin index) and prothrombin value in per cent of the normal This relationship depends not only on the activity of the thromboplastin but also on which type of thromboplastin is used

Another fact which is certainly of significance is that with the oral anticoagulants so far at our disposition it is impossible to attain an ideal and stable effect at all times and in all patients The actual effect achieved varies greatly and this has certainly contributed to the obvious reserve in publishing prothrombin values during treatment

The treatment as judged by the prothrombin values may easily be given with varying degrees of success often partly independent of the influence of the doctor in charge Detailed information in this field would therefore be of interest and is also necessary as a basis for the evaluation of the point at issue in this investigation

Dicoumarol affects coagulation indirectly by reducing the synthesis of prothrombin and proconvertin in the liver thus reducing the concentration of these two important coagulation factors in the blood The effect of dicoumarol can therefore be measured most accurately by estimating the combined effect of these factors as is done directly with Owren s method

Before we go over to an account of the PP values estimated by Owren s method during the treatment of the patients in this investigation a few simple facts of significance in the evaluation of the recorded data will be discussed

Relationship between the PP values recorded and the PP level over the total period of treatment

The first question to be asked is whether the distribution of the PP values recorded corresponds to the proportion of the observation time that these values were present

It should be pointed out that if at two consecutive clinics we find two different PP values we cannot be certain that throughout the intervening period the value has remained between the two values found For example if we find a PP value of 20 % at one clinic and 14 days later it is 35 % we cannot know for certain much less prove that during these 14 days the PP value has always been between 20 and 35 %

However there is reason to believe although we cannot prove it that the PP value has in fact been between the values found at the clinics What we have to rely on here is experience

All those who have had a fairly large number of out patients being treated with anticoagulants will have had the experience of patients who telephone and ask to change their appointment The author has often had this experience and he

has found that the PP values at these unexpected clinics have not shown alterations or unforeseen fluctuations larger than those found at regular clinics at a set hour and day.

An exception from this general rule as regards PP values between clinics is the *after swings* after large alterations of dosage which we see most often in short term treatment. For example if we have made a large increase in the dose and thus caused a steep fall in the PP value from 40 to 10 % often even though we then immediately reduce or withhold dicoumarol the value falls further over the following hours or days to for example 8 % before the increase begins. The same thing in the opposite direction may happen after a steep rise of the PP graph because the dose has been too small even if a large increase in the dose is made immediately the high PP value is found. This is a natural result of the action of dicoumarol which is protracted and has a delayed onset. This has been discussed in more detail in a previous paper by the author (*Bjerkelund* 1953).

During successful long term treatment these after swings are of relatively little importance unlike swings during short term treatment when large initial doses are used. We can therefore state that as far as long term treatment is concerned there will be no error of importance if we reckon that the PP values in the interval between the clinics have been between the two values found at the clinics.

As mentioned earlier the interval between PP estimations has varied both from time to time in individual patients and from one patient to the next. With the uncertainty as regards the PP values in the interval between two clinics in mind it was not considered necessary or appropriate to count each day in each of the 11 648 intervals between the clinics in this investigation. The question therefore becomes what is the relationship between the distribution of different PP values recorded and the proportion of the period of treatment that these different values were present?

It is obvious that this will differ depending on whether we look at treatment in the investigation as a whole or at treatment of the individual cases. As mentioned earlier (see p 103) the supervision of the out patients was at first weekly and later in some cases for the rest of the time fortnightly but patients *who had an especially stable and ideal therapeutic level* were gradually allowed to go for 3 weeks and exceptionally (during holidays) 4 weeks between clinics. A result of this must be that *amongst the total number of PP values for all patients there will be an overrepresentation of the less satisfactory values* as patients with such values attended clinics more frequently.

If we now look at the PP values recorded during the treatment of each individual patient the same could be true but to a lesser extent. The extent to which an overrepresentation of unsatisfactory or satisfactory PP values can make its influence felt will then mostly depend on whether the treatment has been more or less stable and effective during one period than another. If we assume

that the treatment has been as satisfactory in a given period with relatively short intervals between clinics as it has been in a period with longer intervals between clinics there will be good agreement between the distribution of the different PP values and the proportion of the treatment period that these values were present Unsatisfactory values in a period when there are relatively frequent clinics are distributed among many observations and therefore have less bearing on the final picture than if they had occurred in a period with less frequent clinics

If on the other hand the treatment has been noticeably unsatisfactory in the period when the estimations are most frequent we might get for each individual patient a tendency to overrepresentation of too high or too low values However as the supposition when the interval between clinics was prolonged was that the treatment had been stable for a long time there is reason to believe that *an overrepresentation of unsatisfactory values will not have much influence when considering individual cases* An overrepresentation of *satisfactory* values will certainly not take place as the interval between clinics was always shortened when reduced stability was indicated by too high or too low PP values

During the observation time some patients were admitted to hospital because of deterioration of their cardiac condition (recurrent infarction heart failure etc) or because of some complicating disease During such admissions to hospital the PP values were usually estimated 3 times a week in accordance with the usual routine for cases in hospital At these times there were often alterations in the tolerance to dicoumarol and it was not found that treatment in hospital was more intensive or satisfactory than the normal treatment of the same patient when ambulant These admissions to hospital were therefore of no significance in connection with the question of PP values in the period of treatment discussed above Dosage of dicoumarol was during such admissions regulated by the author

Interruptions in treatment

All those who have had experience of long term use of dicoumarol in out patients will know that it is often difficult to maintain a stable therapeutic level Apart from this which is an inherent weakness of the treatment itself there are in patients who are treated for several years now and then complicating circum stances which necessitate a temporary more or less complete interruption in treatment An operation is the most typical reason for such an unavoidable inter ruption Although experience has shown that an operation (assuming meticulous haemostasis) *can* be carried out while dicoumarol is being taken without very great risk on the whole major operations are usually an indication for a tem porary break in the use of dicoumarol so that the PP value becomes normal or nearly normal before the operation starts This is usually an express wish on the part of the surgeon The treatment was in fact usually stopped if major opera tions were necessary

On the other hand some patients had to be operated on as emergencies Appendicectomy was performed while dicoumarol was being used in a 74 year old man and a 68 year old woman when the PP values were 18 and 14 % respectively Both were given ½ litre blood during the operation There were no complications Minor surgery such as tooth extractions etc were also often carried out without interrupting the treatment or just reducing the dose slightly so that the PP value rose to 40–50 %

Another important reason for unavoidable reduction of the dose or possibly a temporary interruption in the treatment was haemorrhage from a pathological process such as an ulcer or cancer in the gastro intestinal tract If such a process is demonstrated or if there is good reason to suspect its presence continued use of anticoagulants constitutes a definite increased risk of serious haemorrhage An interruption in the treatment is indicated until the situation is clearer

Type of material

Many workers investigating long term treatment with anticoagulants state that their patients are carefully selected In contrast to this in the present investigation the patients represent a cross section of cases of infarction aged under 76 years who were able to attend the out patient clinic The investigation includes as mentioned earlier patients at all levels of the intellectual economic and social scales

It was considered necessary to mention this as it entails increased difficulties and makes more demand on the physician in charge especially if the treatment lasts for several years In the present study on account of the nature of the problem under investigation such difficulties could not be waived but the plan had to be followed to the bitter end in all cases

Influence of the problem under investigation on the treatment

The fact that the motive of the treatment was to obtain an answer to a given question has certainly influenced the way in which it was carried out The question was whether or not the antithrombotic effect of dicoumarol measured by estimating the PP value of the blood could influence the prognosis after myocardial infarction If the treatment during the therapeutic trial was going to have no effect the author considered it imperative to be able to exclude the possibility that it had not been sufficiently intensive Therefore the treatment was made as intensive and as stable as possible The administration of dicoumarol was thus probably carried out more intensively and consequently made more demand on the physician in charge than would have been usual if the treatment had not had such a motive

A rather more detailed picture of the antithrombotic effect during the period of treatment as indicated by the registered PP values will now be given

The PP values recorded

Reckoning from the beginning of the observation time in each individual case either to 1st February 1956 or until death there were in the 119 patients in the treated group 11 649 estimations of PP values during a total observation time of 418 33 years The average interval between estimations was thus 12 9 days These figures include however a few short admissions to hospital when the estimations were done 3 times a week The average interval between estimations in *out patients* is therefore really a little longer

Table 47 shows the direct distribution of the total number of PP values recorded in the observation period expressed in per cent It is seen that 81 57 % of the PP values were less than 30 % of normal and 18 43 % were 30 % or over It is also seen that almost half the total values (45 50 %) were between 10 and 19 %

TABLE 47
The direct percentage distribution of 11 649 PP values recorded during the observation time

PP value range (%)	0–9	10–19	20–29	30–39	40–49	50–69	70–
Number of values (%)	8 54	45 50	27 53	10 18	4 38	2 76	1 11

A more correct picture of how the sum of the observation times is distributed between the different PP values is obtained as follows the total number of PP values for each individual patient during the period of treatment was counted and entered in the PP ranges used in Table 47 and 48 The figures for the distribution for each patient were then converted to percentages In this way it was possible to *compare* how large a proportion of the observation time (or any unit of time) fell in each of the PP ranges in the different cases Finally each individual patient s distribution was given a weight figure corresponding to the proportion of the total observation time covered by each case In order to make the distribution as accurate as possible the period of treatment for each individual patient was reckoned in number of days (1 year = 360 days 1 month = 30 days)

Table 48 shows the distribution of the total observation time over the different PP ranges chosen A comparison of these figures with those in Table 47 shows that the postulated overrepresentation of the least satisfactory values does influence the direct distribution of the PP values registered but perhaps to a lesser extent than expected This agrees with the fact that the treatment in most cases was relatively even and stable so that the less satisfactory values which

TABLE 48

The percentage distribution of the total period of treatment 418 33 year at different degrees of anti thrombotic effect as indicated by PP values

PP value range (%)	0–9	10–19	20–29	30–39	40–49	50–69	70–
Proportion of the total period of treatment (%)	8.26	45 65	28 53	9 87	4 17	2 51	1 01

were occasionally observed in some patients do not have much influence on the whole

The figures in Table 48 show that the author has succeeded in making the treatment fairly strict and stable Thus it can be calculated that during the total period of treatment for all the patients the PP values were less than 30 % for 82 44 % of the period and 30 % or more for 17 56 % of the period In 92 31 % of the total period of treatment the PP value was less than 40 % The fact that for almost half the time (45 65 %) the PP value was in the range 10–19 % shows that the treatment was fairly intensive It is therefore not surprising either that it was not so very rare for the PP value to be under 10 % in fact during 8 26 % of the period of treatment it was less than 10 %

Hellem (1952) reported on the use of dicoumarol in 47 patients with an average observation time of approximately 5 months (varying between 19 and 331 days) He found that the PP values had been 40 % or less for 80 % of the total period of observation Treatment in the present investigation has thus been considerably more intensive

Tulloch and Wright (1954) have published the intensity of the treatment with dicoumarol in those out of a total of 182 patients whose prothrombin values had been estimated once a week The prothrombin time was estimated by Quick s method—normal value 14–16 seconds The total duration of the treatment was 142 5 years These authors found that the prothrombin time had been prolonged to 25 seconds or more (40–50 % prothrombin activity or less) for 56 7 % of the total period of treatment (The equivalent values of prothrombin time to percentage of prothrombin activity are stated by Wright See *Wright Bourgain et al* 1954) The results obtained in 53 patients treated with tromexan were considerably less satisfactory

It follows that the treatment in the present group of patients has been much more intensive than that achieved by Tulloch and Wright although they tested their patients once a week

In order to illustrate the stability during effective dosage of dicoumarol the distribution of the treatment period in the different PP ranges has been calculated after exclusion of the intentionally high values obtained when there were interruptions in the dosage for surgical procedures or during complicating disease with a bleeding tendency The corrected distribution is shown in *Table 49* It is

TABLE 49

The percentage distribution of the total period of treatment during effective dosage at the different PP ranges The high values during unavoidable interruptions in treatment have been deducted

PP value range (%)	0–9	10–19	20–29	30–39	40–49	50–69	70–
Corrected proportion of the total period of treatment (%)	8 35	46 18	28 89	9 82	3 96	2 20	0 60

seen that with the technique of dosage used in a non selected group of patients the PP value was kept under 30 % for 83 42 % of the time and under 40 % for 93 24 % of the time

It can be mentioned that in 25 patients in the treated group a total of 33 minor and major operations were carried out during the observation time More details are shown in *Table 50*

TABLE 50

Operations during the treatment period

Tooth extraction and dental surgery	17
Incised abscess	3
Removal of nasal polyps	1
Cataract	1
Operation and later enucleation of an eye after injury	1
Inguinal hernia	3
Appendicectomy	2
Nephrectomy (hypernephroma)	1
Prostate biopsy	1
Prostatectomy	2
Orchidectomy	1
Total	33

PP level in each individual patient

As stated earlier the stability of the effect of the dosage of dicoumarol can sometimes vary significantly from one case to the next It is therefore interesting to investigate how the treatment has been carried out in each individual patient so that we can get an impression of the difference in the effect between the least and the most satisfactory cases

Table 51 shows the distribution of patients by how large a portion of the period of treatment the PP level was less than 30 % i e 29 % or less It is seen that this desirable effect was obtained during the whole period of treatment in

4 cases for 90–100 % of the period in 34 cases and for 80–100 % in 78 cases In only 13 cases was this effect obtained during less than 70 % of the period of treatment In the third column in the same table one can see the distribution of the patients after exclusion of the intentionally high values which occurred as a result of interruption or reduction of the dose because of an operation or a complicating disease with a bleeding tendency These corrected figures thus give an impression of the PP level when the dosages were effective and show that the desired antithrombotic PP level (less than 30 %) was obtained during the whole period in 6 cases for 90–100 % of the period in 39 cases and for 80–100 % in 84 cases

TABLE 51

Distribution of patients by how large a part of the period of treatment (in per cent) the PP level was less than 30 % The column at the right shows the distribution when *the dosages were effective i e when intentionally high PP values as* a result of interrupted or reduced dosage during operations or complicating diseases with a bleeding tendency were disregarded

Per cent of time with PP level less than 30 %	Number of cases	Number of cases corrected for interruptions in treatment
100	4	6
90–99	30	33
80–89	44	45
70–79	28	22
60–69	9	9
50–59	3	3
40–49	1	1
Total number of cases	119	119

Table 52 shows the distribution of the patients by how large a percentage of the period of treatment the PP level was less than 40 % i e 39 % or less It is seen that this effect was obtained for the whole period in 15 cases for 90–100 % in 81 cases and for 80–100 % in 112 cases The corresponding corrected figures are 20 88 and 112 cases respectively

Waaler (1956) investigated the intensity of the long term treatment with anticoagulants (dicoumarol and phenylindanedione) in 275 patients with angina pectoris in Owren s material He found that in 83 of these patients the treatment was "good i e 69 % or over of the recorded PP values were 30 % or less in 152 the treatment was mediocre i e 39 % or over but under 69 % of the PP values were 30 % or less and in 40 patients the treatment was poor i e under 39 % of the PP values were 30 % or less

TABLE 52

Distribution of patients by how large a part of the period of treatment (in per cent) the PP level was less than 40 % The column at the right shows the distribution when the dosages were effective i e when intentionally high PP values as a result of interrupted or reduced dosages during operations or complicating diseases with a bleeding tendency were disregarded

Per cent of time with PP level less than 40	Number of cases	Number of cases corrected for interruptions in treatment
100	15	20
90–99	66	68
80–89	31	24
70–79	6	6
60–69	1	1
Total number of cases	119	119

It follows that the treatment in the present group of patients has been much more intensive as approximately 106 of the 119 cases apparently belong to Waaler s category of good treatment and none to his group of poor treatment (See Table 51)

Anticoagulant therapy in the control group

As previously mentioned this investigation did not include the question of the effect of anticoagulant therapy in the acute phase of myocardial infarction Therefore according to plan the patients in the control group would not be deprived of such treatment if they developed signs of a new acute myocardial infarct (recurrent infarct) They would then again be given anticoagulants during the acute phase i e the first weeks after the attack

It was desirable that anticoagulant therapy should as far as possible only be given to cases where the diagnosis of a new infarct was considered to be certain In practice it was difficult to attain this ideal If a patient is admitted for an attack of praecordial pain it will often be a few days before one can verify the diagnosis Treatment was therefore started in some cases who on further observation came under the heading angina pectoris or acute coronary insufficiency In such cases however treatment was stopped after a week or two as soon as the diagnosis became clear

Anticoagulant therapy in the control group was in all cases only given as short term therapy while in hospital Out patient long term treatment was not started in any of the patients

In all such short term treatment was given to 28 patients in the control group for a total of 36 short periods The total period of treatment was 797 days and

the individual periods varied between 1 day and 52 days the average being about 22 days

The following were the indications for short term therapy in the 36 periods of treatment

Definite recurrent infarct	26 cases
Wrongly diagnosed acute infarct	1 –
Angina pectoris acute coronary insufficiency	7 –
Pulmonary embolism	1 –
Acute thrombophlebitis	1 –
Total	36 cases

It is shown that a clinical thromboembolic condition was the indication for treatment in 28 of the periods of treatment In 1 case anticoagulants were given to a patient who shortly after he had been treated in one department for an acute infarct was admitted to another department for dyspnoea and symptoms of bronchitis The electrocardiographic findings which had appeared with the infarct he had just had were considered to be due to a new infarct

Only for 7 periods in 6 patients was anticoagulant therapy given for angina pectoris or coronary insufficiency where the diagnosis of recurrent infarction could not be verified The total period of treatment in these cases was 103 days the average being barely 15 days Heparin was given initially in 2 of these periods for 1 and 2 days respectively

Seen in relation to the total period of observation in this investigation the periods of prophylactic treatment almost disappear and there will be no noticeable error if they are disregarded when comparing the incidence of recurrent infarction in the treated and control groups

On the other hand it must be assumed that short term treatment of recurrent infarcts in the control group has reduced the mortality and incidence of thromboembolic complications in relation to the infarcts However this is correct and desirable as it is the prophylactic effect of long term and not of short term treatment that is to be investigated

Summary and conclusion

In this chapter an account has been given of the intensity of the anticoagulant therapy in the treated group as judged by the PI values recorded during the observation time This has been done because the author believes that it is very important as a basis for assessing the prophylactic effect of such treatment Information about the intensity of the treatment is only exceptionally given in

previous publications The available information gives reason to believe that one could not expect a better and more stable effect in out patient treatment with dicoumarol of a non selected group of patients than that shown here In other words the antithrombotic effect of dicoumarol is considered to have been used to the full and its possible prophylactic effect could probably not be increased

Finally an account is given of the use of anticoagulants in the control group which was chiefly confined to short term treatment of recurrent infarcts during the observation period

the individual periods varied between 1 day and 52 days the average being about 22 days

The following were the indications for short term therapy in the 36 periods of treatment

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The clinical diagnosis of recurrent infarction

The same diagnostic criteria were used for the diagnosis of new infarctions during the observation period as those used in the diagnosis of the original infarct (see pp 48–49)

The electrocardiographic findings after recurrent infarction are not always so typical and conclusive as after the first infarct However infarcts in a completely new area will usually be as easy to recognise as the original infarct But new infarcts in the area previously infarcted which represent an extension of the earlier infarct are sometimes difficult to verify electrocardiographically A previous infarct may have caused such deformation of the electrocardiogram that possible new alterations will not be recognised This is the case for example with a persisting left bundle branch block electrocardiogram

It is of importance that the diagnosis of complications occurring during the observation period could not always be done with the help of the full diagnostic apparatus Certainly patients with serious complications were almost without exception readmitted to hospital There were however some patients who died suddenly or in the short interval before admission In some of these cases the diagnosis was confirmed at post mortem

It is clear that there was not an equal chance of establishing the diagnosis in all cases The details of the criteria for diagnosis of recurrent infarction will now be mentioned The general lines followed will be given first and then the distribution of the recurrent infarcts between the different grades of diagnostic certainty

(I) *Definite* recurrent infarcts included cases with obvious typical clinical and electrocardiographic findings and were in agreement with the criteria on page 49

(II) *Very probable* recurrent infarcts included

(1) Cases admitted to hospital for long standing severe pain typical in character and localisation who showed typical objective clinical and laboratory findings but where there were few or atypical electrocardiographic changes or where the changes were difficult to judge on account of previous changes

(2) Cases who died at home or elsewhere outside hospital after a typical attack of pain as described under 1 These cases were only included in this group if direct information could be obtained either from those present during the attack and death or possibly from a doctor present indicating that the cause of death was a new infarct In collecting these data a very thorough case history was taken to exclude cardiac deaths for other reasons especially heart failure Cases of sudden death were only included as recurrent infarcts if definite signs of a fresh infarct were found at post mortem These cases together with all the cases mentioned above where the diagnosis was verified at autopsy were reckoned as definite infarcts—group I

(III) *Probable* recurrent infarcts included cases with long standing possibly

repeated typical attacks of pain where objective clinical and electrocardiographic signs were present but not completely convincing

Cases of acute coronary insufficiency possible with corresponding electrocardiographic changes but without objective clinical signs of infarct were not included in this group (see next page)

Table 53 shows the number and distribution of recurrent infarcts during the *observation period for the whole of section B grouped according to the certainty* of the diagnosis It is shown that in 60 patients a total of 73 recurrences were observed 26 in the treated group and 47 in the control group

Before looking at these figures more closely a discussion of the diagnosis of these 73 cases of recurrence is in place It was briefly as follows

In the 26 cases of recurrence in the *treated group* the diagnosis was made during admissions to Ullevål Hospital in 22 cases at the out patient clinic on clinical and electrocardiographic examination by the author in 2 cases and after death at home in 2 cases In one of these last two cases the author examined the patient at home about one hour before and again shortly after death In the other case the author was called shortly after the patient got his fatal attack and arrived immediately after death

TABLE 53

The number of cases with clinically and/or pathologically diagnosed recurrent infarction the number of deaths amongst these cases and the number of recurrences observed in the treated and control groups graded according to diagnostic certainty

Grade of diagnostic certainty	Treated group (119 cases) No cases with recurr	No deaths	No obs recur	Control group (118 cases) No cases with recur	No death	No obs recur
Definite recurrent infarction (Grade I)	14	6	17	29	16	35
Very probable recurrent infarction (Grade II)	5	3	6	6	5	8
Probable recurrent infarction (Grade III)	3	0	3	3	0	4
All grades	22	9	26	38	21	47

Of the 47 cases of recurrence in the *control group* the diagnosis was made during admissions to Ullevål Hospital in 36 cases during admissions to other medical departments in Oslo City Hospitals in 4 cases by the author at the out patient clinic on the clinical and electrocardiographic findings in 2 cases and on the basis of personally collected information in cases of death outside the hospital in 5 cases In one of these last cases the diagnosis was confirmed at autopsy Autopsy was also carried out on all cases of death in the hospital

In addition to the cases of recurrent infarction mentioned above attacks of retrosternal pain in which the diagnosis of myocardial infarction was *suspected* were observed during the observation period in a number of cases As thorough clinical and electrocardiographic examination in these cases did not disclose objective signs of acute infarction they were diagnosed as acute coronary insufficiency or angina pectoris In the treated group 17 such attacks were observed in 11 patients and in the control group 29 attacks in 23 patients —In 13 *of the 17 cases in the treated group and in 23 of the 29 cases in the control group* the patients were thoroughly examined during admissions to hospital in connection with the attack In the remaining 4 cases in the treated and 6 cases in the control group clinical and electrocardiographic examinations were carried out by the author in the out patient clinic Further statistical analysis of these attacks of suspected recurrent infarction will not be carried out It should be pointed out however that such attacks were almost twice as frequent in the control group as in the treated group The ratio between the treated and control group is thus roughly speaking nearly the same for the incidence of these attacks as for the attacks of diagnosed recurrent infarction

From the above mentioned data it is clear that there was a very good chance of making a substantiated diagnosis of recurrent infarction in this investigation For this reason and because of the relatively strict criteria for the diagnosis even in grade III of diagnostic certainty it is believed that there is a good foundation for the diagnosis in all these cases Thus there will be no source of error if the comparison and statistical analysis of the results are based on the total number of patients with recurrence (or the total number of recurrences) without considering the grade of diagnostic certainty It is of advantage to avoid division of the already small groups into even smaller sub groups and it is probable that the results using larger groups are more correct and dependable

Table 53 shows that in all 60 patients had a recurrence during the observation period Of the 119 patients in the treated group 22 had a recurrence (18 5 %) while for the 118 patients in the control group there were 38 recurrences (32 %)

Of the 60 patients who had a recurrent infarct there were 11 who had *more than one recurrence* In the treated group there were 4 definite recurrences in one patient and 2 recurrences in another The first patient had had 4 infarcts previously including the one which included her in the investigation In the control group there were 9 patients who each had 2 recurrences in the observation period As the table shows there was a total of 73 recurrences 26 in the treated group 9 of which were fatal and 47 in the control group 21 of which were fatal

It is clear from these figures that both the incidence of recurrence and the mortality from recurrence are considerably higher in the control than in the treated group Roughly it can be said that the number of patients who had a recurrence and the incidence of recurrence in the treated group is 3 of that in the control group and that the mortality from recurrence in the treated is half

repeated typical attacks of pain where objective clinical and electrocardiographic signs were present but not completely convincing

Cases of acute coronary insufficiency possible with corresponding electrocardiographic changes but without objective clinical signs of infarct were not included in this group (see next page)

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The number of cases with clinically and/or pathologically diagnosed recurrent infarction the number of deaths amongst these cases and the number of recurrences observed in the treated and control groups graded according to diagnostic certainty

Grade of diagnostic certainty	Treated group (119 cases) No. of cases with recurr.	No. of deaths	No. of obs. recurr.	Control group (118 cases) No. of cases with recurr.	No. of deaths	No. of obs. recurr.
Definite recurrent infarction (Grade I)	14	6	17	29	16	35
Very probable recurrent infarction (Grade II)	5	3	6	6	5	8
Probable recurrent infarction (Grade III)	3	0	3	3	0	4
All grades	22	9	26	38	21	47

Of the 47 cases of recurrence in the *control group* the diagnosis was made during admissions to Ullevål Hospital in 36 cases during admissions to other medical departments in Oslo City Hospitals in 4 cases by the author at the out patient clinic on the clinical and electrocardiographic findings in 2 cases and on the basis of personally collected information in cases of death outside the hospital in 5 cases In one of these last cases the diagnosis was confirmed at autopsy Autopsy was also carried out on all cases of death in the hospital

the sexes separately in the statistical analysis of the incidence of recurrence The relatively small numbers also make it undesirable to subdivide the groups too much for analysis

TABLE 55

Relationship between force of recurrence and sex

	\o a	Av ge (years)	T t l durat n f e p u e to risk (ye)	No es w th recu	F e of recurren e /mille/yea
Treated group					
Men	88	57 6	305	16	52
Women	31	63 3	93	6	65
Control group					
Men	93	58 5	243	29	119
Women	25	62 0	78	9	115

Relationship between recurrent infarction and age

Table 56 shows the number of patients with recurrences and the total number of recurrences observed in the treated and control groups in relation to the age on admission for the first recorded acute infarct It is seen that in section B there were 113 patients of 60 years and over Of these 37 had recurrences and 19 died There were 124 patients under 60 years of whom 23 had recurrences and 11 died These figures seem to indicate that the danger both of recurrence and of death is greater in the higher age groups As has been shown previously when the prognosis was discussed and as would moreover be expected the age is related to both the incidence of recurrence and the mortality This is also seen clearly if we examine the treated and control groups separately

TABLE 56

Relationship between recurrent infarction and age of patient on admission

Age g o p (y)	N case	T t d g up No with e u r	N b c	N c	C nt l g up N ca with r u r	N obs i r
30–39	1	0	0	4	0	0
40–49	16	0	0	14	3 (2)	3
50–59	44	8 (3)	8	45	12 (6)	18
60–69	47	12 (6)	16	36	14 (9)	15
70–75	11	2	2	19	9 (4)	11
All ages	119	22 (9)	26	118	38 (21)	47

The figures in brackets refer to the number of deaths

In the treated group there were 58 patients of 60 years and over of whom 14 had recurrences and 6 died and there were 61 patients under 60 years of whom 8 had recurrences and 3 died In the control group there were 55 patients of 60 years and over of whom 23 had recurrences and 13 died and 63 patients under 60 of whom 15 had recurrences and 8 died The age factor is therefore important both in the treated and control groups

Table 56 also shows the total number of recurrences observed in the different age groups

Table 57 gives a general picture of the number of patients with recurrences and the number of deaths in relation to both age and sex It needs no further explanation

It follows from the above that age in this investigation as in others is a factor of great prognostic significance It is therefore obvious that this must be taken into consideration in the further analysis and evaluation of the results

TABLE 57

Relationship between recurrent infarction and the sex and age of patient

Age group (years)	Treated group: Men, No. cases	Treated group: Men, No. with recurr.	Treated group: Women, No. cases	Treated group: Women, No. with recurr.	Control group: Men, No. cases	Control group: Men, No. with recurr.	Control group: Women, No. cases	Control group: Women, No. with recurr.
30–39	1	0	0	0	4	0	0	0
40–49	15	0	1	0	14	3 (2)	0	0
50–59	37	5 (2)	7	3 (1)	33	9 (4)	12	3 (2)
60–69	27	10 (5)	20	2 (1)	29	11 (7)	7	3 (2)
70–75	8	1	3	1	13	6 (3)	6	3 (1)
All ages	88	16 (7)	31	6 (2)	93	29 (16)	25	9 (5)

The figures in brackets refer to the number of deaths

Statistical examination of the incidence of recurrent infarction

A statistical comparison of the incidence of recurrent infarction in the treated and control groups will now be made First it must be made clear that this comparison only covers the first recurrence observed in each patient As mentioned previously some patients both in the treated and control group had more than one recurrence during the observation period It is obvious though that the incidence of these secondary recurrences should not be included with the incidence of the first recurrence without more ado Once a patient has had one recurrence there is a worsening of the prognosis and the correct thing to do then is to make a separate comparison of these patients However the figures for second ary and subsequent recurrences in this investigation are so small that they cannot be judged statistically

The statistical analysis of the comparability of the two groups gave a satisfactory result (see chapter VI) During the subsequent analysis it can therefore be assumed that the 119 patients in the treated group were chosen by drawing lots among the 237 patients in section B

Each patient is followed from the beginning of the observation period either to death or to the end of the observation period

When investigating the recurrences three causes of withdrawal are reckoned with

Cause of withdrawal I Recurrent infarction After the patient has had his first recurrence he is withdrawn from this statistical calculation

Cause of withdrawal II Death with cause other than infarction

Cause of withdrawal III End of observation time

The *duration of exposure to risk* for a patient is calculated from the time he is taken under observation until he is withdrawn The most this period could be was 72 months It has been subdivided into interval both short (see Tables 58–61) and longer (0–12 months 12–30 months 30 months–) The duration of exposure to risk for a patient in an interval is the proportion of his total duration of exposure to risk which falls in the interval For each interval the sum of the durations of exposure to risk for the patients is calculated

Let the probability that a patient present at time t will be withdrawn before the time t + dt be λdt (where dt is small) λ is then the *force of withdrawal* for the appropriate cause *(force of recurrence or force of mortality)* The conception force of recurrence (force of mortality) is the probability per unit of time at a definite point of time in the observation period that a recurrent infarct (death) will occur Reckoning approximately the size of the force of recurrence is assumed constant in any interval of time under consideration The force can therefore be calculated approximately by dividing the number of cases who are withdrawn for a given cause in an interval by the total duration of exposure to risk in that interval

As the patient s age is important for the incidence of recurrence both the treated and control groups have been subdivided into two groups according to age on admission with the recorded acute infarct Sixty years old was taken as the dividing line There were thus 4 groups to consider (A further subdivision into age groups was considered inadvisable on account of the limited number of patients)

Tables 58–61 give a general picture of the occurrence of recurrent infarction in the groups Each table shows the chronological sequence of the various groups of patients as it would have been if all the patients had come under observation simultaneously and were withdrawn for the three causes having been exposed to risk for the actual intervals present in each case The second column shows how the group of patients became depleted as the observation period progressed Each figure represents the number of patients present at the beginning of the different

TABLE 58

Recurrent infarction in patients under 60 years old
Treated group

Length of interval (months)	No. present at beg. of int.	Total duration of exp. to risk (years)	No. recurr. in interval	No. withdrawn for other causes: Death	End obs. period	Av. age at time 0 for those still present	Force of recurrence /cent. year
0– 1	61	5 01	1	0	0	52 5	20 0
1– 3	60	10 00	0	0	0	52 5	0 0
3– 6	60	15 00	0	0	0	52 5	0 0
6–12	60	29 66	0	1	0	52 5	0 0
12–18	59	28 65	3	0	0	52 4	10 5
18–24	56	27 37	2	2	0	52 2	7 4
24–30	52	25 73	1	0	0	52 1	3 9
30–36	51	25 40	1	0	2	52 0	3 9
36–42	48	30 94	0	0	4	51 8	0 0
42–48	44	18 23	0	0	18	51 5	0 0
48–54	26	8 73	0	0	13	52 9	0 0
54–60	13	4 26	0	0	8	53 8	0 0
60–66	5	1 35	0	0	4	54 2	0 0
66–72	1	0 00	0	0	1	55 0	0 0

TABLE 59

Recurrent infarction in patients under 60 years old
Control group

Length of interval (months)	No. present at beg. of int.	Total duration of exp. to risk (years)	No. recurr. in interval	No. withdrawn for other causes: Death	End obs. period	Av. age at time 0 for those still present	Force of recurrence /cent/year
0– 1	63	5 05	3	2	0	52 0	59 4
1– 3	58	9 39	2	0	0	51 9	21 3
3– 6	56	13 71	1	1	0	51 8	7 3
6–12	54	25 81	3	1	0	51 8	1 2
12–18	50	25 00	0	0	0	51 6	0 0
18–24	50	24 66	1	1	0	51 6	4 1
24–30	48	23 01	2	2	0	51 4	8 7
30–36	44	20 60	1	0	4	51 0	4 9
36–42	39	15 40	1	1	13	51 4	6 5
42–48	24	10 36	0	0	7	50 2	0 0
48–54	17	5 90	1	0	8	50 4	16 9
54–60	8	3 19	0	1	2	51 9	0 0
60–66	5	0 62	0	0	5	51 0	0 0
66–72	0	0 00	0	0	0		0 0

TABLE 60

Recurrent infarction in patients 60 years old and over

Treated group

Length of interval (months)	No. present at beg. of int.	Total duration of exposure to risk (years)	No. recurrences in interval	No. withdrawn for other causes: Death	End obs. period	Average age at time of those still present	Force of recurrence / cent/year
0–1	58	4.61	3	1	0	65.9	65.1
1–3	54	8.74	3	0	0	66.1	34.3
3–6	51	12.75	0	0	0	66.0	0.0
6–12	51	25.22	1	1	0	66.0	4.0
12–18	49	23.94	3	0	0	66.0	13.0
18–24	46	22.76	0	1	0	66.0	0.0
24–30	45	22.03	0	1	0	66.0	0.0
30–36	44	19.50	1	3	5	66.1	5.1
36–42	35	14.67	0	0	9	66.8	0.0
42–48	26	11.57	3	0	5	67.3	25.3
48–54	18	6.64	0	1	8	67.6	0.0
54–60	9	3.37	0	0	5	67.6	0.0
60–66	4	0.49	0	0	4	66.5	0.0
66–72	0	0.00	0	0	0		0.0

TABLE 61

Recurrent infarction in patients 60 years old and over

Control group

Length of interval (months)	No. present at beg. of int.	Total duration of exposure to risk (years)	No. recurrences in interval	No. withdrawn for other causes: Death	End obs. period	Average age at time of those still present	Force of recurrence /cent/year
0–1	55	4.32	5	1	0	67.4	115.7
1–3	49	8.01	2	0	0	67.4	25.0
3–6	47	11.28	4	0	0	67.3	35.5
6–12	43	20.74	2	2	0	67.5	9.6
12–18	39	18.32	2	1	0	67.6	10.9
18–24	36	16.93	2	1	0	67.5	11.8
24–30	33	16.04	1	0	0	67.4	6.2
30–36	32	15.37	0	0	4	67.3	0.0
36–42	28	11.35	2	3	6	66.7	17.6
42–48	17	7.35	3	0	2	66.9	40.8
48–54	12	4.64	0	0	5	66.9	0.0
54–60	7	2.31	0	0	4	65.3	0.0
60–66	3	0.82	0	0	2	66.3	0.0
66–72	1	0.09	0	0	1	68.0	0.0

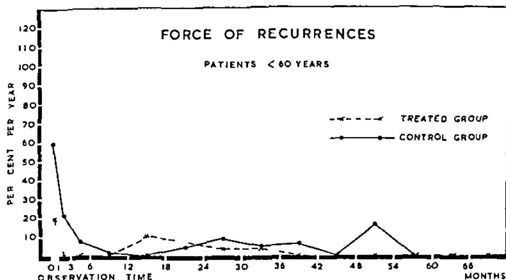
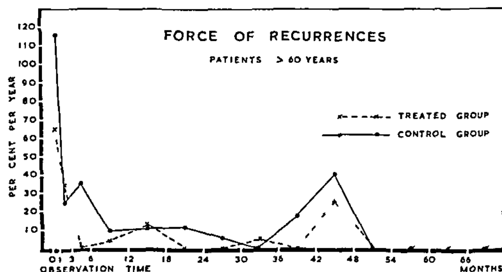

FORCE OF RECURRENCES
PATIENTS < 60 YEARS
TREATED GROUP
CONTROL GROUP
PER CENT PER YEAR
120
110
100
90
80
70
60
50
40
30
20
10
0 1 3 6 12 18 24 30 36 42 48 54 60 66
OBSERVATION TIME
MONTHS

Fig 1


FORCE OF RECURRENCES
PATIENTS > 60 YEARS
TREATED GROUP
CONTROL GROUP
PER CENT PER YEAR
120
110
100
90
80
70
60
50
40
30
20
10
0 1 3 6 12 18 24 30 36 42 48 54 60 66
OBSERVATION TIME
MONTHS

F-2

intervals Column 3 shows the total duration of exposure to risk in the interval Columns 4–6 show the number of patients withdrawn for the three causes The second to last column shows the average age on admission with the recorded acute infarct for those still present at the beginning of each interval

Each group was very heterogenous as regards age and there might therefore be a certain danger that the age composition would alter as the observation period progressed (e g it was predominately the oldest who were withdrawn) In this way the forces of recurrence would not be comparable towards the end of the period But as shown in the second to last column there is nothing to indicate that this has taken place

The last column shows the average force of recurrence in the various intervals Here one should naturally not put too much weight on the individual figures as they are based on very few observations (see column 4) Looking at the figures as a whole they show in spite of large chance variations a certain trend in the observation period which can also be seen graphically in *Figs 1 and 2* This trend *is also apparent in the summary shown in Tables 62 and 63 and Figs 3 and 4*

TABLE 62

Recurrent infarction in patients under 60 years old

	Treated group			Control group		
Length of interval (months)	Total duration of exposure to risk (years)	No recurr	Force of recurrence /cent/y	Total duration of exposure to risk (years)	No recurr	Force of recurrence /cent/year
0–12	59.7	1	2	54.0	9	17
12–30	81.8	6	7	72.7	3	4
30–	88.9	1	1	56.1	3	5

TABLE 63

Recurrent infarction in patients 60 years old and over

	Treated group			Control group		
Length of interval (months)	Total duration of exposure to risk (years)	No recurr	Force of recurrence /cent/year	Total duration of exposure to risk (years)	No recurr	Force of recurrence /cent/year
0–12	51.3	7	14	44.3	13	29
12–30	68.7	3	4	51.3	5	10
30–	56.2	4	7	41.9	5	12

The force of recurrence in the control group seems to be largest initially (probably for the first 6 months) *In the treated group this initial "excess of recurrences is not present in patients under 60 years old* However in patients 60 and over this effect of the treatment cannot be seen so clearly After 12 months there is no statistical difference between the forces of recurrence in the treated and control groups

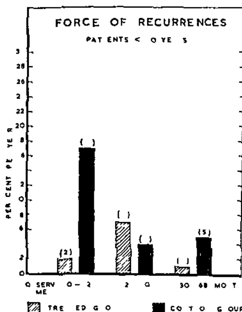


Fig 3

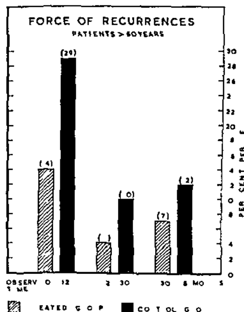


Fig 4

Testing statistical significance

The difference in the forces of recurrence in the two groups in *the first 12 months* is tested by calculating $z = -2$ times the logarithm of the likelihood ratio and using *Wilks rule* (1938) for the sampling distribution of this variable. Large values of z indicate a systematic difference.

For the force of recurrence in the groups under 60 years old $z = 8.15$. The probability of getting a larger value by chance is $p = 0.4\%$. In the groups 60 years and over $z = 2.8$ and there is a $p = 9\%$ probability for a larger variation by chance. *Using 5 % level there is thus a significant difference between forces of recurrence in the first 12 months for patients under 60.* Twelve months has been chosen arbitrarily. The figures show that it is probable that the tendency is most felt in the first half of this period.

Relationship between incidence of recurrent infarction and other factors of cardiological significance

Before finishing the discussion of the incidence of recurrent infarction it is of interest to try to form an idea of whether or not the force of recurrence is related to factors of cardiological significance other than age. At the same time a rough assessment of the prophylactic significance of anticoagulant therapy in different categories of patients will be made.

It is impossible to apply accurate statistical methods to this subject on account of the limited number of patients involved. However the figures will be able to give an approximate impression evaluated against the background of the results of the detailed statistical calculations and the level of statistical significance just mentioned.

For patients in both treated and control groups the relationship will be investigated between the incidence of recurrence and the existence of the following conditions: angina pectoris or infarct(s) before the observed infarct, hypertension, cardiac enlargement (assessed radiologically) at the beginning of the observation period and finally body weight.

In order to avoid the groups being too small with increased danger of chance variation the simultaneous division into above and below 60 years has been omitted when placing the patients in the different categories. On the other hand the average age for each individual group has been calculated so that the influence of selection as measured by age can be assessed.

Previous angina pectoris

The number of patients suffering from angina pectoris before admission for the investigated infarction has been mentioned previously (see page 64). *Table 64* shows the force of recurrence and the average age in these patients in relation to those who had not previously had angina pectoris—both in the treated and control groups. It is clear that the force of recurrence in these two categories of patients is about the same in the two groups. With due consideration for the possible influence of chance the figures seem perhaps to indicate that anticoagulant therapy does not afford better protection to one category than to the other.

TABLE 64

Relationship between force of recurrence and previous angina pectoris

	No cases	Average (years)	Total duration of exposure to risk (years)	No of cases with recurrence	Force of recurrence /mill/year
Treated group					
Angina pectoris	57	59.4	194	10 (3)	52
No angina pectoris	62	58.6	204	12 (5)	59
Control group					
Angina pectoris	*66*	*59.6*	*181*	*24 (12)*	133
No angina pectoris	52	58.7	139	14 (4)	101

The figures in brackets refer to the number of patients who died as a result of their first recurrent infarct.

Previous infarction

Table 65 shows the force of recurrence and the average age of patients who had had one or more infarcts before the investigated infarct in comparison with those who had not—both in the treated and control groups (see also p 64) The number of patients who had had previous infarcts is small in both groups and it is therefore very probable that chance has influenced the figures They do however seem to indicate that the force of recurrence is larger in patients who had had a previous infarct in both treated and control groups and anticoagulant therapy does not seem to have protected these patients much Thus in this respect the present investigation differs from that of *Suzman Rushm and Goldberg* (1955) who found that long term therapy is specially indicated in patients who have had several previous infarcts

TABLE 65

Relationship between force of recurrence and previous infarction

	No cases	Av age (years)	Total duration of exposure to risk (years)	No cases with recurrence	Force of recurrence /mille year
Treated group					
Previous infarct	16	59 3	40	8 (4)	200
No previous infarct	103	59	358	14 (4)	39
Control group					
Previous infarct	11	56 9	27	7 (4)	259
No previous infarct	107	59 4	293	31 (12)	106

The figures in brackets refer to the number of patients who died as a result of their first recurrent infarct

Blood pressure

As mentioned earlier (see pp 99–102) the blood pressure was recorded regularly at the clinical cardiological follow up clinics of the patients in both groups For reasons mentioned in the same place the pressure was measured slightly more frequently and regularly in the control than in the treated group *Throughout the whole observation period about 1 180 measurements were taken* in the 118 patients in the control group and about 670 measurements in the 119 patients in the treated group Most of the measurements were made by the investigator at the follow up clinics after the patients had sat quietly while the case history was brought up to date usually for 15–30 minutes and subsequently lain on a flat couch for routine examination If hypertension was found the measurement was always made 2–3 times usually with a few minutes interval in between Some measurements were also made during admissions to hospital in the observation time

As acute myocardial infarction is often accompanied by a fall in blood pressure and not infrequently the blood pressure remains low for several weeks or months grouping of infarction patients according to their blood pressure is especially difficult Such periods with lower blood pressure were recorded in many of the patients in this study both after the first observed acute infarct and after possible later infarcts in the observation period before it gradually rose to (?) previous possibly high level In assessing the blood pressure levels the investigator found that the correct thing to do was to disregard the labile periods in relation to the acute infarct provided that the observation period was sufficiently long and the measurements frequent enough for this to be possible In some patients who died early in the observation period the assessment and grouping of the blood pressure had to be done using measurements before the first observed acute infarct during the course of the infarct and possibly a few later measurements By using all the available data there has been a good basis for the grouping in nearly all cases

The patients have been divided into 3 categories according to the general representative level of the blood pressure (1) Patients with normal blood pressure This group includes patients in whom each time the blood pressure was measured the diastolic pressure was never over 90 mm and the systolic pressure never over 150 mm Hg (2) Patients not in either group 1 or 3 (3) Patients with definite diastolic hypertension This group included patients who each time the blood pressure was measured had a diastolic pressure of 100 mm Hg or more —Group 2 chiefly included patients with systolic hypertension but also some with labile swinging blood pressure and a couple of cases who were difficult to classify on account of scarcity of information

TABLE 66

Relationship between force of recurrence and blood pressure

	No case	A ge (y s)	T t l durati n of p u t sk (ye s)	N s with ecurrenc	F of recu n e /m ll /y a
Treated group					
Normal BP	28	55 4	103	2 (1)	19
Syst hypertension	57	60 3	191	12 (3)	63
Diast hypertension	34	59 8	104	8 (4)	77
Control group					
Normal BP	26	58 3	70	7 (3)	100
Syst hypertension	57	59 8	150	17 (8)	113
Diast hypertension	35	58 6	100	14 (5)	140

The figures in b ackets refer to the number f pat nts who d ed as a result of the r first recurre t infarct

Table 66 shows the force of recurrence in patients in the treated and control groups in relationship to the 3 categories just mentioned The figures show a very slight but systematic increase of the force of recurrence with increase of blood pressure which is true both for the treated and control groups However con sidering the previously mentioned level of statistical significance the difference is very small and not much weight can be attached to it The difference between treated and untreated cases is largest in group 1 there the force of recurrence in treated patients with normal blood pressure is very low about ⅕ of that in untreated cases It should however be noted that the average age of these treated patients with normal blood pressure is significantly lower than that in the control group and this selection may account for the difference in the effect of the treatment

Size of the heart

The size of the heart of patients in this investigation has been mentioned previously (see pp 84–86) It was measured radiologically at the beginning of the observation period This is discussed on page 86 where the limits taken for normal possibly enlarged (border line) and definitely enlarged hearts are given The patients are thus divided into 3 categories according to the size of the heart and a fourth small group where comparative data were lacking

Table 67 shows the force of recurrence for each of these categories The figures show that the force increases markedly and systematically with increasing cardiac volume both in the treated and control groups The individual groups are small and the observed data so sparse that the difference probably does not constitute statistical proof with the level of significance used But the difference is so marked and systematic in both groups that it seems reasonable to believe that it is not purely a matter of chance

The effect of anticoagulant therapy seems to have no relationship to the size of the heart For all the 3 categories of cardiac volume the force of recurrence is roughly twice as large in the control as in the treated group

The highest force of recurrence is found in the small group of patients where radiological data were lacking for grouping at the beginning of the observation period (Subsequently collected data were not considered comparable or of any use for this grouping) One of the reasons for scarcity of data was that some of these patients were at that time so weak after their acute infarct that they were spared the ordeal of the relatively exhausting radiological investigation (which also included outdoor transport to another department) Some were unable to go through with the investigation making it impossible to get pictures suitable for measurement of cardiac volume In 3 out of 6 examined patients in the treated group and 4 out of 5 in the control group a later X ray showed a significantly enlarged heart

TABLE 67

Relationship between recurrent infarction and size of the heart estimated radiologically

Cardiac volume	No. of cases	Av. age (years)	Total duration of exposure to risk (years)	No. of cases with recurrence	Force of recurrence /mille/year
Treated group					
Normal	81	58 0	293	10 (2)	34
Border line	18	59 9	56	5 (1)	89
Enlarged	11	62 3	24	3 (3)	125
Not measured	9	62 7	25	4 (2)	160
Control group					
Normal	74	57 9	229	19 (6)	83
Border line	20	61 9	49	7 (2)	143
Enlarged	17	61 2	29	8 (6)	276
Not measured	7	60 9	13	4 (2)	308

The figures in brackets refer to the number of patients who died as a result of their first recurrent infarct

Body weight

The prognosis after myocardial infarction has often been related to obesity and it has also been suggested that marked over weight involves increased risk of thrombosis (see e g *Wright Marple and Beck* 1954 pp 235–238) In this study therefore the force of recurrence for patients in both treated and control groups has been examined in 3 different weight categories These categories were made using Broca s formula for the height weight relationship as follows –0 0–9 10– (See pp 63–64)

Table 68 shows the grouping of the patients according to weight and the force of recurrence in each category in both the treated and control groups The figures give no indication that there is any relation between force of recurrence and body weight Among the patients who are more than 10 kg over weight the force of recurrence in the treated group is relatively low whereas in the control group it is relatively high so that the difference between the treated and control patients of this category is fairly great It can therefore be asked whether this might indicate that the prophylactic effect of anticoagulant therapy in obese patients is especially good If we look at the figures again we see that there was only one recurrence in obese patients in the treated group and the force of recurrence in this category is also definitely lower than that in the other *treated* groups On the whole there is therefore good reason to believe that this difference may be a matter of chance

TABLE 68

Relationship between incidence of recurrent infarction and body weight

Height weight relation	No. cases	Av. age (years)	Total duration of exposure to risk (years)	No. cases with recurrence	Force of recurrence /mille/year
Treated group					
–0	50	58.9	160	12 (6)	75
0–9	41	58.9	139	9 (2)	65
10–	28	60.9	99	1	10
Control group					
–0	45	58.5	112	13 (7)	116
0–9	51	59.3	152	13 (6)	86
10–	22	60.5	56	12 (3)	214

The figures in brackets refer to the number of patients who died as a result of their first recurrent infarct.

Summary

In this chapter the new infarcts diagnosed during the observation period in the treated and control groups are discussed. The criteria for the diagnosis, the degree of certainty of the diagnosis and the incidence of recurrence in the two groups and its relation to sex and age are mentioned.

A statistical investigation is also made of the "force of recurrence", i.e. the probability per unit of time at a definite point of time in the observation period that a recurrent infarct will occur. It has been shown that *using 5 % level the force of recurrence for patients under 60 years old is significantly higher in the control than in the treated group during the first 12 months of the observation period.* The difference between forces of recurrence in patients 60 years and over in the same period has the same trend but has no statistical significance. After 12 months there is no definite difference between the groups either over or under 60.

An exploratory investigation has been made of the force of recurrence after grouping the patients according to different factors which might be thought important for the tendency to recurrence, and in this way the effect of treatment has been illustrated from different points of view. There seems to be evidence that the force of recurrence is especially high in patients who have had several previous infarcts and dicoumarol therapy does not seem to have protected these patients much. It was also found that the force of recurrence increases with increasing cardiac volume.

A more detailed discussion of the observed data and their significance in the evaluation of long term therapy will follow in Chapter XVIII.

CHAPTER XI

Mortality during the observation period
Statistical analysis of the mortality

Mortality together with the incidence of recurrence is the most important factor when trying to assess the effect of long term anticoagulant therapy in patients who have survived an acute myocardial infarct These two phenomena do not vary independently of each other As will be seen soon the occurrence of a new infarct was the cause of death in many of the patients in this investigation However apart from intercurrent diseases patients with coronary disease can die as a result of many other pathological processes in the cardiovascular system besides coronary occlusion Examples include heart failure cerebral vascular accidents (thromboembolic or haemorrhagic) and generalised arteriosclerosis with the possibility of secondary thrombosis in different organs These processes might be directly or indirectly affected by anticoagulant therapy An investigation into the mortality will therefore give the most comprehensive and significant indication of the effect of treatment

In all there were 66 deaths in the 237 patients in section B i e about 28 % Of these there were 24 deaths in the 119 patients in the treated group (i e approx 20 %) and 42 in the 118 patients in the control group (i e approx 36 %)

The causes and circumstances of death in all these 66 patients were as follows

Treated group Of the 24 deaths in the treated group 19 occurred in hospital and 5 outside Of the 19 who died in hospital 15 died in one of the medical departments in Ulleval Hospital 1 died on the way to hospital and 2 died suddenly at the author s follow up clinic Autopsy was carried out in all these cases Finally 1 patient died in another hospital She had had 8 certain infarcts of which 4 were recurrent infarcts during the observation time and she had been treated by the author over a long period for invaliding chronic heart failure and angina pectoris Before death she had been diagnosed as heart failure cardiac cachexia and generalised arteriosclerosis Autopsy was not carried out in this case

Of the 5 deaths outside hospital 3 occurred at home and 2 (sudden deaths) elsewhere Autopsy was carried out in one of the latter 2 cases Of the 3 cases who died at home there was one case of sudden death where the author was given an exact description by the patient s wife a few days later In the 2 other cases death occurred with typical symptoms of a new infarct One of these patients was examined by the author one hour before and again shortly after death In the

other case the author was summoned immediately the symptoms started and arrived about half an hour later a few minutes after death had occurred

Control group Of the 42 deaths in the control group 23 occurred in hospital and 19 elsewhere

Of the 23 who died in hospital 18 died in one of the medical departments at Ullevål Hospital and one died on the way to hospital There were 4 cases who died in medical departments of other Municipal Hospitals in Oslo Autopsy was performed in 22 of the 23 cases who died in hospital In one case autopsy was not permitted but this patient died of an acute intercurrent disease (acute yellow atrophy of the liver)

Of the 19 who died outside hospital there were 12 who died at home and 7 elsewhere In 2 of the last cases the author was able to arrange an autopsy In all the 19 cases of death outside hospital the author collected an accurate case history including the circumstances of death from conversation with the nearest relations or others present during the last illness and/or death In many cases death was notified to the author by the relatives who often visited the hospital for this purpose In some cases supplementary information was obtained from a doctor who had either treated the patient at home or been called for the last illness or death

It follows that in all cases of death in the observation time there was relatively good evidence on which to diagnose the cause of death

The cause of death was verified at post mortem in 43 of the 66 cases 19 out of 24 cases in the treated group and 24 out of 42 cases in the control group More details about the patients who died will be given now and in Chapter XVII

Causes of death

As already mentioned 24 patients died in the treated group and 42 in the control group One gets the immediate impression that the mortality in the treated group is only 4/7 as large as in the control group or that long term therapy has prevented or postponed 3/7 of the deaths A detailed investigation is however needed in order to be able to assess these figures Before continuing with the statistical examination of the mortality in the treated and control groups the causes of death will be mentioned and also the relationships between mortality and sex and age as these are of great interest for the statistical analysis

Table 69 gives a general picture of the different causes of death and the number of deaths in the treated and control groups The table shows that the cause of death was nearly always cardiovascular i e 23 in the treated and 38 in the control group Only 5 of the 66 patients died of an intercurrent disease 1 in the treated and 4 in the control group

Recurrent infarction (certain or very probable) was the cause of death in 9 cases in the treated and 21 cases in the control group Autopsy was carried out

TABLE 69

Number of deaths during the observation period Causes of death

Cause of death	Treated group 119 cases	Control group 118 cases
Certain recurrent infarction	6	17
Probable recurrent infarction	3	4
Ruptured heart	1	0
Ruptured ventricular septum	0	1
Sudden death	5	9
Heart failure	2	4
Cerebral haemorrhage	4	1
Generalised arteriosclerosis with sec complications	2	2
Intercurrent disease	1	4
Total number of deaths	24	42

in 7 cases in the treated and 17 in the control group In 3 of these cases in the treated group and 2 in the control group death occurred instantaneously or in a few minutes but post mortem showed signs of a new infarct so they were classified as such and not as sudden death

Ruptured heart as a cause of death was verified at autopsy in 2 cases in the treated group One of these patients presented with clinical signs of a severe recurrent infarct with marked shock 9 days before death This case was therefore included under recurrent infarction in the table Pathological signs of fresh infarct were rather difficult to assess because of marked deformity due to previous infarction with an aneurism like bulging of the wall of the ventricle and haemorrhage in the wall round the rupture aperture All the same slight recent degenerative changes and a fresh coronary thrombosis were demonstrated In the other case death occurred instantaneously 3 weeks after the beginning of the observation period At autopsy neither recent signs of infarction nor fresh thrombotic occlusion were demonstrated

Rupture of the ventricular septum was the cause of death in 1 patient in the control group The diagnosis was made in life when the patient was *admitted* shortly before death and was confirmed at autopsy This case has been *published* earlier *(Bjerl elund and Gundersen* 1951)

Sudden death was considered as the cause of death in 5 cases in the treated and 9 cases in the control group Autopsy was carried out in 4 of these cases (3 treated and 1 control) but neither signs of a fresh infarct nor of fresh thrombotic coronary occlusion were demonstrated In addition to the 14 cases mentioned here there were 6 cases mentioned earlier where the true cause of death was shown at autopsy The *type of death* was thus sudden death in 20 cases altogether 9 in the treated and 11 in the control group

Chronic heart failure was the cause of death in 2 cases in the treated group one of whom had a post mortem In addition heart failure with persisting oedema and pleural effusion was a contributory cause of death in one case At post mortem however a very enlarged heart was found with signs of a severe old infarct but also signs of fresh infarction In the control group heart failure was the cause of death in 4 patients but none had autopsies Three of these patients had been treated for a long time by the author for severe chronic heart failure by a salt restricted diet digitalis mercurial diuretics etc Two of them had valvular as well as coronary disease (rheumatic mitral and aortic valvular disease and aortic stenosis respectively) The fourth had had hypertension and mild signs of heart failure even before the acute infarct and had chronic heart failure after discharge from hospital He died 10 months later

Cerebral haemorrhage was the cause of death in 5 cases 4 in the treated and 1 in the control group The diagnosis was confirmed at autopsy in all these cases They will be mentioned later in Chapter XIII

Generalised arteriosclerosis with secondary complications was the cause of death in 4 patients 2 in each group Post mortem was carried out in all of these four cases

Both of the two patients in the treated group had terminal cachexia cerebral symptoms (confusion apathy and somnolence) and clinical signs of uraemia At autopsy in both cases severe diffuse arteriosclerosis was found in the following sites (1) cerebral arteries—old areas of softening in the brain (2) severe coronary sclerosis and fibrosis of the myocardium (old infarcts) with enlarged heart and in one case aneurism of the heart (3) arterio and arteriolosclerosis in the kidneys and (4) diffuse sclerosis of the aorta and large arteries In one of these cases sclerosis with fresh thrombosis was also found in the femoral arteries In this case dicoumarol had been stopped in the 6–8 weeks before death because of diminishing mental capacity and lack of cooperation

Of the two corresponding patients in the control group one had previously had two recurrent infarcts during the observation period He also got terminal obliterating arteriosclerosis with acute secondary thrombosis in the femoral artery and gangrene of a toe Shortly afterwards he had a cerebral thrombosis with persisting hemiparesis and marked reduction of mental capacity The other patient had 9 months before death a severe cerebral vascular accident with persisting total paralysis of the left side and he died with signs of bronchopneumonia and pulmonary oedema At autopsy in both these patients severe arteriosclerosis and a very large area of softening in the brain were found Further atheroma and old occlusions in the coronary arteries with diffuse fibrosis (old infarcts) in the myocardium were present In the first case the following were also found a pedunculated thrombus attached to the wall of the left ventricle near the apex arteriosclerosis and occluding thrombosis in the left common iliac artery and thrombosis in the right renal artery but without complete occlusion

This patient had anticoagulant therapy during the acute phase of the two recurrent infarcts in the observation period and also when he had a third suspected but not verified infarct He did not get it with the terminal thrombotic complications as his condition was then considered intractable

In concluding the discussion of the cardiovascular causes of death it will be mentioned that of the 23 deaths in the treated group 4 patients had had one recurrent infarct and 1 had had four recurrences earlier in the observation period Of the 38 deaths in the control group there were 8 patients who had had one recurrent infarct and 1 who had had two previous recurrent infarcts

Intercurrent disease was the cause of death in 1 patient in the treated group who died of a cerebral tumor (glioblastoma multiforme) and 4 patients in the control group who died of acute yellow atrophy of the liver myelomatosis malignant cylindroma of the trachea with metastases and cancer of the pharynx respectively All these 5 cases were diagnosed in hospital 4 died in hospital and 3 had post mortems

Relationship between mortality and sex

Table 70 shows the number of deaths amongst men and women in the treated and control groups In the whole of section B there were 181 men of whom 51 (approx 28 %) died and 56 women of whom 15 (approx 27 %) died Excluding the 5 cases where intercurrent disease was the cause of death the figures for men and women are 47 (26 %) and 14 (25 %) respectively In the whole of section B the mortality is therefore very similar in men and women It is however rather different if we consider the treated and control groups separately In the treated group 17 % of the men and 26 % of the women and in the control group 34 % of the men and 24 % of the women died of cardiovascular disease

TABLE 70

Relationship between mortality and sex

	Treated group		Control group	
	No. cases	No. deaths	No. cases	No. deaths
Men	88	15	93	36 (4)
Women	31	9 (1)	25	6

The figures in brackets refer to the number of deaths due to intercurrent disease

It seems therefore that the mortality of the women in this investigation is the same regardless of treatment but in the men treatment reduces the mortality by about a half

The same is seen if we investigate the force of mortality as is shown in *Table 71* However the difference is very small considering the level of statistical significance used (see later)

TABLE 71

Relationship between force of mortality and sex

	No cas	Av age (years)	Duration of exposure to risk (years)	No deaths	Force of mortality /mille/year
Treated group					
Men	88	57 6	319	15	47
Women	31	63 3	99	9 (1)	81
Control group					
Men	93	58 5	274	36 (4)	117
Women	25	62 0	87	6	69

The figures in brackets refer to the number of deaths due to intercurrent disease These are excluded from the calculation of the force of mortality

It is probable that the difference depends on chance because of the relatively small numbers involved This probability is strengthened if we compare these figures with those for force of recurrence (pp 124–125) where there was no evidence that treatment was more effective in men than in women The fact that 3 women in the treated and 1 in the control group died of cerebral haemorrhage has also influenced the small numbers

On the whole there is no reason to subdivide the groups according to sex for the further investigation of the mortality especially as further subdivision would complicate and probably diminish the value of the statistical investigation

Relationship between mortality and age

Table 72 shows the number of patients and the number of deaths in the treated and control groups arranged according to age It is seen that in section B there was a total of 113 patients of 60 years old and over of whom 39 died and 124 patients under 60 of whom 27 died These figures show in agreement with all previous clinical experience that the prognosis is worse in the higher age groups

This is also clear if we look at the treated and control groups separately

In the treated group there were 58 patients of 60 and over of whom 16 died and 61 patients under 60 of whom 8 died

In the control group there were 55 patients of 60 years old and over of whom 23 died and 63 patients under 60 of whom 19 died

Table 73 gives a general picture of the number of patients and the number of deaths arranged both according to age and sex It needs no further explanation

It follows from the above that age in this study as in others is a factor of great prognostic significance It is obvious that it must be taken into account during the further analysis and evaluation of the results

TABLE 72

Relationship between mortality and the age of the patients on admission

Age group (years)	Treated group No. cases	Treated group No. deaths	Control group No. cases	Control group No. deaths
30–39	1	0	4	0
40–49	16	1	14	5
50–59	44	7	45	14 (1)
60–69	47	14 (1)	36	15 (2)
70–75	11	2	19	8 (1)
All ages	119	24 (1)	118	42 (4)

The figures in brackets refer to the number of deaths in the group due to intercurrent disease

TABLE 73

Relationship between mortality and the sex and age of the patients on admission

Age group (years)	Treated group Men No.	Treated group Men No. deaths	Treated group Women No. cases	Treated group Women No. deaths	Control group Men No.	Control group Men No. deaths	Control group Women No. cases	Control group Women No. deaths
30–39	1	0	0	0	4	0	0	0
40–49	15	1	1	0	14	5	0	0
50–59	37	5	7	2	33	12 (1)	12	2
60–69	27	8	20	6 (1)	29	12 (2)	7	3
70–75	8	1	3	1	13	7 (1)	6	1
All ages	88	15	31	9 (1)	93	36 (4)	25	6

The figures in brackets refer to the number of deaths in the group due to intercurrent disease

Statistical examination of the mortality

A statistical investigation and comparison of the mortality in the treated and control groups will now be made. For this comparison it has been considered most correct to disregard the 5 deaths due to intercurrent disease, i.e. 1 case in the treated and 4 in the control group. The causes of death in these 5 cases have already been mentioned and none of them had any relation to the treatment. Therefore, when considering the mortality in the light of the effect of treatment, these deaths are best excluded, especially as the figures are not the same in the two groups.

The statistical analysis of the mortality is carried out in exactly the same way as the investigation into the incidence of recurrent infarction (see pp. 126–132).

Each patient is followed from the beginning of the observation period either till death or to the end of the observation period. The three following causes of withdrawal are reckoned with:

Cause of withdrawal I Death of cardiovascular disease

Cause of withdrawal II Death of intercurrent disease (very few)

Cause of withdrawal III End of observation period

The duration of exposure to risk for a patient is reckoned from the time he is taken under observation until he is withdrawn

As with recurrent infarction both the treated and control group have been divided into two sub groups according to the age on admission with the recorded acute infarct and 60 years is taken as the dividing line There are thus 4 groups to consider

Tables 74–77 give a general picture of the mortality in these groups Each table shows the chronological sequence of the various groups of patients as it would have been if all the patients had come under observation simultaneously and were withdrawn for the three causes having been exposed to risk for the actual intervals present in each case The second column shows how the group of patients became depleted as the observation period progressed Each figure represents the number of patients present at the beginning of the different intervals Column 3 shows the total duration of exposure to risk in the interval Columns 4–6 show the number of patients withdrawn for the three causes The second to last column shows the average age on admission with the recorded acute infarct for those still present at the beginning of each interval Each group was very heterogenous as regards age and there might therefore be a certain danger that the age composition would alter as the observation period progressed (e g it was predominately the oldest who were withdrawn) In this way the force of mortality might not be comparable towards the end of the period But as shown in the second to last column there is nothing to indicate that this has taken place

The last column shows the average force of mortality in the various intervals Here one should naturally not put too much weight on the individual figures as they are based on very few observations (see column 4)

Looking at the figures as a whole they show in spite of large chance variations a certain trend in the observation period which can also be seen graphically in *Figs 5 and 6*

This trend is also shown in *Tables 78 and 79* which are a summary of the larger tables and in *Figs 7 and 8*

The force of mortality seems to be largest initially (probably especially in the first 6 months) in the control group *In the treated group this initial excess mortality is not present in patients under 60 years* This effect of the treatment is not seen so clearly for patients 60 years and over

After 12 months there is no statistical difference between the force of mortality in the treated and control group

TABLE 74

Mortality in patients under 60 years old
Treated group

Length of interval (months)	No. present at beg. of int.	Total duration of exposure to risk (years)	No. deaths of cardiovascular disease	No. withdrawn for other causes: Deaths from other diseases	No. withdrawn for other causes: End obs. period	Average time 0 for those still present	Force of mortality /cent/y
0– 1	61	5.08	0	0	0	52.5	0.0
1– 3	61	10.00	1	0	0	52.5	10.0
3– 6	60	15.00	0	0	0	52.5	0.0
6–12	60	29.66	1	0	0	52.5	3.4
12–18	59	29.33	1	0	0	52.4	3.4
18–24	58	28.23	3	0	0	52.3	10.6
24–30	55	27.20	1	0	0	52.2	3.7
30–36	54	26.62	1	0	2	52.2	3.8
36–42	51	23.68	0	0	5	52.0	0.0
42–48	46	19.01	0	0	19	51.7	0.0
48–54	27	9.02	0	0	13	52.9	0.0
54–60	14	4.51	0	0	9	53.8	0.0
60–66	5	1.35	0	0	4	54.2	0.0
66–72	1	0.00	0	0	1	55.0	0.0

TABLE 75

Mortality in patients under 60 years old
Control group

Length of interval (months)	No. present at beg. of int.	Total duration of exposure to risk (years)	No. deaths of cardiovascular disease	No. withdrawn for other cause: Deaths from other diseases	No. withdrawn for other cause: End obs. period	Average time 0 for those still present	Force of mortality /cent/y
0– 1	63	5.05	5	0	0	52.0	99.0
1– 3	58	9.67	0	0	0	51.9	0.0
3– 6	58	14.40	1	0	0	51.9	69.4
6–12	57	27.90	2	0	0	52.0	7.2
12–18	55	27.42	1	0	0	52.0	3.6
18–24	54	26.93	0	1	0	52.0	0.0
24–30	53	25.19	3	0	0	52.0	11.9
30–36	50	23.03	3	0	4	51.9	13.0
36–42	43	17.33	1	0	14	52.0	5.8
42–48	28	12.01	1	0	8	51.1	8.3
48–54	19	6.81	0	0	10	51.4	0.0
54–60	9	3.43	1	0	3	53.3	29.2
60–66	5	0.62	0	0	5	53.0	0.0
66–72	0	0.00	0	0	0		0.0

TABLE 76

Mortality in patients 60 years old and over
Treated group

Length of interval (months)	No present at beg of int	Total duration of exp to risk (years)	No deaths of cardio vascular disease	No withdrawn for other cause: Death from other dis	No withdrawn for other cause: End obs period	Av age at time 0 for those still present	Force of mortality /cent/year
0– 1	58	4 07	3	0	0	65 0	73 7
1– 3	55	9 01	1	0	0	66 1	11 1
3– 6	54	13 50	0	0	0	66 2	0 0
6–12	54	26 82	2	0	0	66 2	7 5
12–18	52	25 90	1	0	0	66 1	3 9
18–24	51	25 26	1	0	0	66 1	4 0
24–30	50	24 53	1	0	0	66 2	4 1
30–36	49	21 14	4	1	7	66 3	18 9
36–42	37	15 50	0	0	10	66 9	0 0
42–48	27	12 49	1	0	6	67 5	8 0
48–54	20	6 57	1	0	9	67 4	15 2
54–60	10	3 41	0	0	6	68 0	0 0
60–66	4	0 49	0	0	4	69 0	0 0
66–72	0	0 00	0	0	0		0 0

TABLE 77

Mortality in patients 60 years old and over
Control group

Length of interval (months)	No present at beg of int	Total duration of exp to risk (years)	No deaths of cardio vascular disease	No withdrawn for other causes: Death from other dis	No withdrawn for other causes: End obs period	Av age at time 0 for those still present	Force of mortality /cent/year
0– 1	55	4 48	2	1	0	67 4	44 6
1– 3	52	8 40	2	0	0	67 5	23 8
3– 6	50	12 36	3	0	0	67 3	24 3
6–12	47	23 08	3	0	0	67 5	13 0
12–18	44	21.29	2	0	0	67 6	9 4
18–24	42	20 13	3	0	0	67 6	14 9
24–30	39	19.34	1	0	0	67 5	5.2
30–36	38	18.36	0	0	5	67 5	0 0
36–42	33	13 50	2	2	9	67 1	14 8
42–48	20	9 17	1	0	3	67 1	10 9
48–54	16	6 41	0	0	7	67 4	0 0
54–60	9	3 13	0	0	5	65 6	0 0
60–66	4	0 87	1	0	2	66 8	114 9
66–72	1	0 09	0	0	1	68 0	0 0

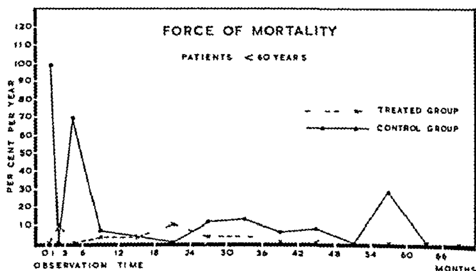

FORCE OF MORTALITY
PATIENTS < 60 YEARS
TREATED GROUP
CONTROL GROUP
PER CENT PER YEAR
120
110
100
90
80
70
60
50
40
30
20
10
0 1 3 6 12 18 24 30 36 42 48 54 60 66
OBSERVATION TIME
MONTHS

Fig 5

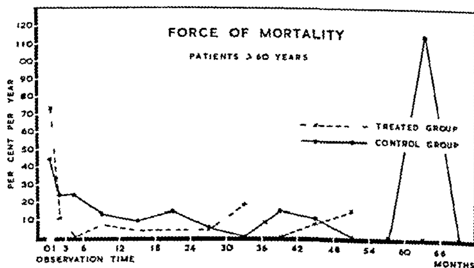

FORCE OF MORTALITY
PATIENTS > 60 YEARS
TREATED GROUP
CONTROL GROUP
PER CENT PER YEAR
120
110
100
90
80
70
60
50
40
30
20
10
0 1 3 6 12 18 24 30 36 42 48 54 60 66
OBSERVATION TIME
MONTHS

Fig 6

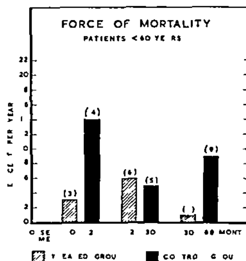


Fig 7

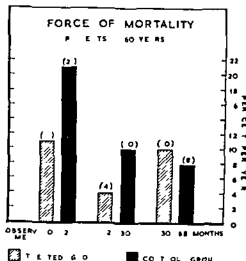


Fig 8

TABLE 78

Mortality in patients under 60 years old

Length of interval (months)	Treated group: Total duration of exposure to risk (years)	No death	Force of mortality /cent/year	Control group: Total duration of exposure to risk (years)	No deaths	Force of mortality /cent/year
0–12	59 7	2	3	57 0	8	14
12–30	84 8	5	6	79 5	4	5
30–	84 2	1	1	63 2	6	9

TABLE 79

Mortality in patients 60 years old and over

Length of interval (months)	Treated group: Total duration of exposure to risk (years)	No death	Force of mortality /cent/year	Control group: Total duration of exposure to risk (years)	No deaths	Force of mortality /cent/year
0–12	53 4	6	11	48 3	10	21
12–30	75 7	3	4	60 8	6	10
30–	59 6	6	10	51 5	4	8

Testing statistical significance

The difference in the force of mortality in the two groups in *the first 12 months* is tested by calculating $z = -2$ times the logarithm of the likelihood ratio and using *Wald's rule* for the sampling distribution of this variable Large values of z indicate a systematic difference For the force of mortality in the groups under

60 years old $z = 4.1$ The probability of getting a larger value by chance is $p = 4.2\%$ In the groups 60 years and over $z = 1.5$ and there is a $p = 22.6\%$ probability for a larger chance variation *Using 5 % level there is thus a significant difference between forces of mortality in the first 12 months for patients under 60 years* Twelve months has been chosen arbitrarily The figures show that it is probable that the tendency is most felt in the first half of this period

Relationship between mortality and different factors of cardiological significance

Before leaving the subject of mortality it is of interest to examine the relationship between the force of mortality and the effect of treatment in the different cardiological categories of patients previously mentioned in connection with the force of recurrence (see pp 132–138) This aspect of the investigation is only expected to give a rough idea of the trends and its results will not be able to be subjected to accurate statistics However the figures will be able to give an approximate impression evaluated against the background of the results of the detailed statistical calculations and the level of statistical significance mentioned previously

Previous angina pectoris

Table 80 shows the force of mortality in the treated and control groups in patients who had had angina pectoris before the investigated infarct and those who had not The figures show that there is no certain evidence of any difference between these two groups either as regards mortality or effect of treatment

TABLE 80

Relationship between mortality and previous angina pectoris

	No. cases	Av. age (years)	Total duration of exposure to risk (years)	No. deaths	Force of mortality /milli/y
Treated group					
Angina pectoris	57	59.4	204	11	54
No angina pectoris	62	58.6	214	13 (1)	56
Control group					
Angina pectoris	66	59.6	195	25	128
No angina pectoris	52	58.7	165	17 (4)	79

The figures in brackets refer to the number of deaths in each group due to intercurrent disease. These deaths are excluded from the calculation of the force of mortality

TABLE 81

Relationship between mortality and previous infarction

	No cases	Av age (years)	Total duration of exposure to risk (years)	No deaths	Force of mortality /mille/year
Treated group					
Previous infarct	16	59 6	45	7	156
No previous infarct	103	59 0	373	17 (1)	43
Control group					
Previous infarct	11	56 9	29	6	207
No previous infarct	107	59 4	331	36 (4)	97

The figures in brackets refer to the number of deaths in each group due to intercurrent disease These deaths are excluded from the calculation of the force of mortality

Previous infarction

Table 81 shows the force of mortality in the treated and control groups in patients who had had one or more infarcts before the investigated infarct and those who had not

It is clear that the force of mortality is considerably larger in patients who had had several infarcts both in the treated and control groups This is in agreement with the results of several previous investigations of the prognosis after infarction Although on account of the small groups the difference is probably not significant it may not be purely a matter of chance

Several authors (see Wright Nichol etc) have previously presumed that long term anticoagulant therapy is especially indicated in patients with recurrent infarction This has also been maintained by *Suzman Ruskin and Goldberg* (1955) The figures in the present study give no support to this theory It seems on the contrary that the treatment is most effective in patients who have only had a single infarct Unfortunately the investigation is too small to provide the final answer to this question (See also p 134)

Blood pressure

The grouping of the patients according to blood pressure has previously been mentioned (see pp 134–136)

Table 82 shows the force of mortality in the patients in the treated and control group after division into the same blood pressure groups The figures do not give any indication that the blood pressure has any influence on the mortality in the observation period The effect of treatment seems to be best in the group with normal blood pressure like the results found in connection with the force

TABLE 82

Relationship between mortality and blood pressure

	No. of cases	Av. age (years)	Total duration of exposure to risk (years)	No. of deaths	Force of mortality [illegible]
Treated group					
Normal BP	28	55 4	105	2	19
Syst hypertension	57	60 3	204	13 (1)	59
Diast hypertension	34	59 8	110	9	82
Control group					
Normal BP	26	58 3	80	8 (1)	88
Syst hypertension	57	59 8	170	22 (2)	118
Diast hypertension	35	58 6	111	12 (1)	99

The figures in brackets refer to the number of deaths in each group due to intercurrent disease These deaths are excluded from the calculation of the force of mortality

of recurrence The relatively low average age of the patients in the treated group with normal blood pressure is probably of importance in connection with this difference

Size of the heart

The grouping of the patients according to the size of the heart where the volume is estimated radiologically is mentioned on pages 84–86 and page 136

Table 83 shows how the force of mortality in both groups increases with increasing heart volume similar to the results found in the calculation of the force of recurrence The relatively large differences and their systematic appearance in both the treated and control groups make it very likely that it is not a matter of chance This is also in good agreement with clinical experience but is seldom mentioned in previous investigations into the prognosis in patients with coronary disease

The effect of treatment seems to be best in the group with normal cardiac volume The difference between the treated group and the control group here is so large that it is probably not purely due to chance However the lower average age of the patients with normal hearts is probably also of importance in causing this difference As shown earlier the effect of long term treatment with dicoumarol in this investigation is better in patients under 60 years than in those of 60 years and over

Body weight

The grouping of the patients according to body weight is the same as that previously mentioned (see pp 63 and 137)

TABLE 83

Relationship between mortality and size of heart estimated radiologically

Cardiac volume	No. cases	Av. age (years)	Total duration of exposure to risk (years)	No. deaths	Force of mortality /mille/year
Treated group					
Normal	81	58.0	305	6 (1)	16
Border line	18	59.9	61	8	131
Enlarged	11	62.3	24	6	250
Not measured	9	62.7	28	4	143
Control group					
Normal	74	57.9	253	19 (3)	63
Border line	20	61.9	59	7 (1)	102
Enlarged	17	61.2	32	12	375
Not measured	7	60.9	17	4	235

The figures in brackets refer to the number of deaths in each group due to intercurrent disease. These deaths are excluded from the calculation of the force of mortality.

Table 84 shows the force of mortality in the treated and control groups after division of the patients into the weight classes. The figures give no indication that weight has any relation to mortality in this investigation and there is no evidence that the difference in the effect of treatment apparently shown by the figures is really more than chance variation.

TABLE 84

Relationship between mortality and body weight

Height weight relation	No. cases	Av. age (years)	Total duration of exposure to risk (years)	No. deaths	Force of mortality /mille/year
Treated group					
–0	50	58.9	170	12	71
0–9	41	58.9	149	7	47
10–	28	60.9	99	5 (1)	40
Control group					
–0	45	58.5	126	17 (1)	127
0–9	51	59.3	169	17 (3)	83
10–	22	60.5	66	8	121

The figures in brackets refer to the number of deaths in the group due to intercurrent disease. These are excluded from the calculation of the force of mortality.

Summary

In this chapter the mortality in the treated and control groups has been discussed The circumstances of death the number of post mortems carried out and other information leading to the diagnosis of the cause of death in each case have been mentioned The relationship between mortality and both age and sex has been examined

A statistical analysis has then been carried out of the force of mortality i e the probability per unit of time at a definite point of time in the observation period that death will occur This showed that *using 5 % level the force of mortality in patients under 60 years is significantly higher in the control group than in the treated group in the first 12 months of the observation period* The difference between forces of mortality in patients 60 years and over in the same period is much less and has no statistical significance After 12 months there is no certain difference between the groups either over or under 60

Finally an exploratory investigation has been made of the force of mortality after having grouped the patients according to different factors which might be of prognostic significance In this way the effect of treatment has been illustrated from different points of view

There seems to be evidence that the mortality is relatively high in patients who have had several previous infarcts and that the mortality increases with increasing heart volume

Anticoagulant therapy seems to be more effective in patients with a normal than with an enlarged heart and more effective in patients who have only had a single infarct than in those who have a history of two or more previous infarcts The significance of the observed data in the evaluation of long term therapy will be discussed in chapter XVIII

CHAPTER XII

PP level in relation to recurrent infarction and sudden death

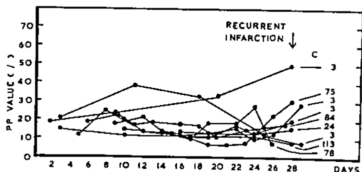
The PP level in relation to the occurrence of thromboembolic episodes during long term anticoagulant therapy is of considerable theoretical and practical interest. Information of this sort is very scanty in previous publications partly because the intensity of the long term treatment as a whole is usually not given. Here therefore a special effort was made to find out whether and if so to what extent a decrease in the intensity of the treatment has been the cause of the recurrent infarcts and sudden deaths.

The PP value was recorded in direct relation to 24 of the 26 recurrent infarcts in the treated group. In the other 2 cases only two days had elapsed since the last PP value had been taken.

Of the 5 cases of sudden death in the treated group the PP value in direct relation to the episode was known in 3 cases as the investigator had the opportunity of obtaining a sample of blood by cardiac puncture shortly after death. In the other 2 cases 6 and 9 days had elapsed since the last PP value but in both these cases treatment had been ideal for a long time with a very stable PP level around 20 %.

When the question of the relation of the PP level to a thromboembolic episode is to be investigated it is not enough to look at the PP value in direct relation to the episode alone. Theoretically it is possible that the thrombotic process started slightly before it became clinically manifest. It is therefore also necessary to look at the PP level in the period preceeding the actual episode.

Figures 9, 10 and 11 show the PP graphs in the weeks before each of the 26 cases of recurrent infarction in the treated group. It is shown that marked increases to 70 % (2 days before the episode) and 68 % were present in 2 cases (case 66, Fig. 10 and case 34, Fig. 11). The first of these two patients had however previously had a recurrent infarct when the PP value was 12 % (Fig. 10). A more moderate increase to values between 30 and 50 % was observed in 5 cases. One of these patients had previously had 3 definite recurrent infarcts when the PP value was 8 %, 20 % and 26 % respectively (see Fig. 9, case 3). Finally in one patient (case 106, Fig. 10) there was an increase to 62 % five days before the infarct occurred as a result of forgetting to take the tablets. In the remaining 18 cases of recurrent infarction treatment was as shown by the figures very stable and satisfactory in the period before the infarct and the infarct occurred with the PP values between 8 % and 29 %.



Fi 9

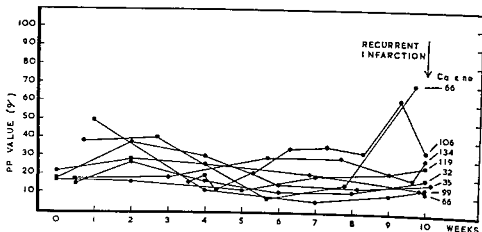
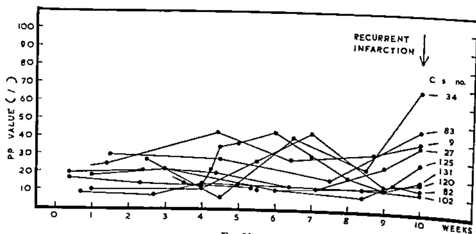


Fig 10



F g 11

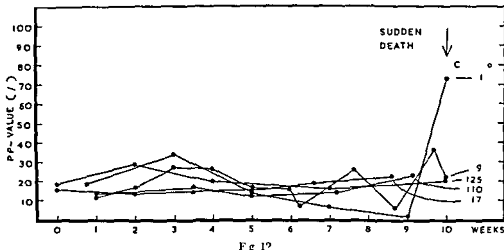


Fig 12

Fig 12 shows the PP graphs in the weeks preceding the five sudden deaths. It is evident that the treatment was very stable and intensive in all cases except one (case 1 Fig 12). This was a patient with familial xanthomatosis who towards the end had severe progressive angina pectoris and a simultaneous decreasing *tolerance to dicoumarol. One week before death the PP value had decreased to* 1 %. Dicoumarol was then withheld for a few days and the dose thereafter drastically reduced. When she attended the out-patient clinic 8 days later sudden death occurred. A sample of blood taken by cardiac puncture showed a PP value of 73 %, but at autopsy there was no sign of fresh coronary thrombosis or of a new infarct.

Table 85 shows the percentage distribution over different ranges of effect of the PP values which were recorded in direct relation to the 31 episodes mentioned above. For comparison with these values the distribution of the PP level in the period of treatment as a whole is given for (1) the patients in whom the episodes occurred and (2) the treated group as a whole. It is evident that PP values of less than 30 % were found in 71 %, 77 % and 82 % respectively in the above three categories.

TABLE 85

PP value per cent	Percentage distribution of PP values: In relation to recurrent infarction and sudden death	In the whole period of treatment in cases of recurrent infarctions and sudden death	In the whole period of treatment for the treated group as a whole
0–29	71	77	82
30–39	13	13	10
40–	16	10	8

As can be seen in this investigation there has only been a very moderate shift toward the higher PP values amongst the cases of recurrent infarction and sudden

death It is possible that these high PP values may have been the cause of the respective episodes in exceptional cases However it must be remembered that the small increases may equally well have been the result of an increased lability in dicoumarol tolerance in relation to a deterioration of the diseas which often preceeded the actual episode

On the whole it can be said that a relatively diminished intensity of treatment has not played any significant part in causing the recurrent infarcts and cases of sudden death in the treated group in this investigation

Summary and conclusion

In this chapter an account has been given of the I P level in relation to the episodes of recurrent infarction and sudden death It is evident that a relatively diminished intensity in the treatment has not played a significant part in causing these episodes

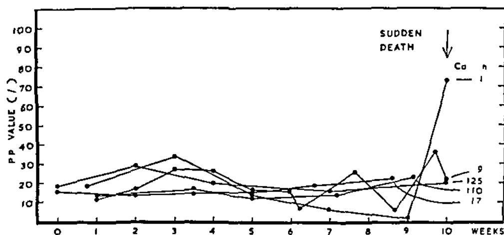


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CHAPTER XIII

Haemorrhagic complications

In Chapter IX it has been shown that the treatment with dicoumarol has been relatively intensive in this investigation. A pertinent question which will now be discussed is therefore: how about haemorrhagic complications during treatment?

First some general remarks. All the patients in the treated group were given careful instructions about the danger of haemorrhage which can result from the treatment. They were told to report at once to the author if they noticed any form of bleeding, i. e. haematuria, epistaxis, blood in faeces or if they noticed signs of bleeding in the skin or mucous membranes.

It must be stated that the haemorrhagic complications that were recorded only included haemorrhages of such a type or such severity that the patient himself noticed it and reported to the author. Neither systematic investigation for microscopic haematuria, the stool benzidine test nor undressing of the patients to look for minor skin haemorrhages were done in out-patients, even if the PP value was low.

Haemorrhages so mild that the patient does not notice them himself are considered to be of no clinical significance and of little practical interest. An exception is of course occult bleeding in the gastro-intestinal tract and chemical or microscopic haematuria secondary to local, possibly malignant disease. Often anticoagulant therapy brings such haemorrhages to notice relatively early (see later).

When a low PP value was observed the patient was usually asked if he had noticed any form of bleeding. In some sensitive nervous patients the question was omitted if possible so as to avoid unnecessary anxiety.

When clinical haemorrhage occurred or when the patient stated that he had noticed bleeding in one form or another, the fact was entered on the patient's PP graph in direct relationship to the PP level when the bleeding occurred.

Number of haemorrhages, type and degree of severity

The haemorrhages have been grouped below both as regards type and severity. There were 3 degrees of severity:

(1) *Mild haemorrhages*. The haemorrhages in this group were so mild that they were of no clinical significance, they did not inconvenience the patient and required no special treatment. Examples include insignificant temporary epistaxis

(possibly in connection with nose blowing during a cold) trifling cutaneous haemorrhages and brief episodes of mild haematuria It was characteristic of such episodes that the patients did not usually consult the author (or any other doctor) when the episode occurred The episodes usually came to light either on examination or they were mentioned spontaneously by the patient at the next clinic If the PP value was found to be low the dose of dicoumarol was reduced or sometimes withheld for a day or two and in some cases an intravenous injection of menadione was given

(2) *Moderate haemorrhages* included cases where the haemorrhage was of such a type or of such severity that the patient was inconvenienced They were not however severe enough to necessitate admission to hospital or blood transfusion Apart from local haemostasis in some cases of epistaxis special treatment was not necessary in this group It was sufficient to reduce the dose of dicoumarol until the PP value reached a slightly higher level if necessary hastened by injecting menadione

(3) *Severe haemorrhages* These included all those that were of such size or type that the patient had to be admitted to hospital for tranfusions local haemostasis and/or because the haemorrhage was accompanied by pain or other serious clinical symptoms

The grouping out lined here was chosen arbitrarily It is hoped that all the same it will be valuable during the discussion of the significance of haemorrhagic complications in this investigation It is obvious that the boundary between mild and moderate haemorrhage is ill defined and often can only be estimated approximately On the other hand the boundary between moderate and severe cases is well defined but it must be remembered that other factors than severe or life threatening haemorrhage may be the reason for an admission to hospital

Table 86 shows in outline the total number of haemorrhagic episodes classified according to type and severity The figures in brackets refer to the number of cases where another (possibly primary) cause of bleeding was found apart from the use of anticoagulants

If all types and grades of haemorrhage are included it is found that in the total period of treatment 418 33 years there were 53 haemorrhagic episodes in 37 of the 119 patients In other words an episode occurred every 7 9 years of treatment per patient

Tulloch and Wright (1954) state that the incidence of haemorrhage in 227 cases with a total treatment time of 180 3 years was one haemorrhage every 2 6 years of treatment per patient i e a significantly higher incidence in spite of the treatment as previously mentioned being less intensive (see p 114)

Foley Devitt Symons and Wright (1954) observed 31 haemorrhagic episodes in 85 patients with a total treatment time of 303 2 years This corresponds to one haemorrhage every 9 8 years of treatment per patient

TABLE 86

Haemorrhagic episodes during treatment with dicoumarol classified according to type and severity

Type of haemorrhage	Severity of haemorrhage Mild	Moderate	Severe
Cutaneous haemorrhage	4 (1)	0	0
Muscle haematoma	0	2 (1)	2
Epistaxis	8	1 (1)	3 (1)
Haematuria	8 (6)	8	3
Haematemesis melaena occult bleeding	0	1 (1)	6 (5)
Rectal bleeding	1 (1)	0	1
Cerebral haemorrhage	0	0	4
Subarachnoid haemorrhage	0	0	1 (1)
Total	21 (8)	12 (3)	20 (7)

The figures in brackets refer to the number of cases in which there was another (possibly primary) cause of haemorrhage apart from anticoagulant therapy

Bay et al (1954) observed haemorrhages in 12 of 115 patients with a total treatment time of 126 5 years i e approximately one haemorrhage every 10 5 years of treatment per patient

Nichol et al (1954) state the incidence of haemorrhagic episodes in 1091 patients with a total treatment time of 2038 years They found haemorrhages in 289 sites in 220 of the patients i e one haemorrhage every 7 1 years of treatment per patient

It is thus apparent that the incidence of haemorrhagic complications in the present material has been approximately the same as that reported by other workers in this field

Waaler (1956) has investigated the incidence of haemorrhagic complications in 275 of Owren s patients on long term anticoagulant therapy Including even the mildest insignificant haemorrhages he found approximately 80 haemorrhagic episodes in a total of 670 years of treatment i e one haemorrhage every 8 4 years of treatment per patient If the mildest episodes were excluded there were 33 moderate or severe haemorrhages This corresponds to approximately one such haemorrhage every 20 years of treatment per patient

If in the present investigation we exclude the mild insignificant haemorrhage we get 32 moderate or severe haemorrhages i e one such haemorrhage every 13 1 years of treatment per patient Thus the incidence of such haemorrhages in the present group of patients is somewhat higher than that found by Waaler This is natural when the greater intensity of the treatment in the present investigation is taken into account (See page 116)

Generally speaking the incidence of haemorrhages during long term treatment with anticoagulants should always be evaluated in relation to the intensity of the treatment if a fair comparison between different investigations is to be made However as mentioned earlier it is only in very exceptional cases that such data are available

Haemorrhages severe enough to necessitate admission to hospital occurred in 20 cases in the present investigation i e once every 21 years of treatment per patient

Relationship between haemorrhages and PP values

In all the severe cases of haemorrhage the PP value was estimated in direct relation to the episode i e actually during the bleeding The same was true of most of the moderate and some of the mild cases But in the remaining moderate and mild cases one was able to get quite a good idea of the PP level at the time of the episodes by considering the PP values recorded beforehand and afterwards For the sake of simplicity the PP level in these cases has been calculated by interpolating between the values found before and after taking into consideration the date that the haemorrhage occurred

Table 87 shows the relationship of the mild moderate and severe haemorrhages to the PP level The figures in brackets refer to the number of cases in which on further investigation another contributory cause of haemorrhage was found apart from anticoagulant therapy The table shows that in about half the total number of haemorrhages and 8 of the moderate and severe haemorrhages the PP value was less than 10 % Of the cases in which a contributory cause of haemorrhage was found apart from anticoagulant therapy ⅓ had PP values less than 10 % and 3 had higher values

TABLE 87

The relationship between haemorrhagic complications and PP values

PP value per cent	No. of cases of haemorrhage Mild	Moderate	Severe	Total
0– 4	1	3	5 (1)	9 (1)
5– 9	5	5 (1)	7 (3)	17 (4)
10–19	7 (2)	3 (1)	7 (2)	17 (5)
20–29	8 (6)	0	1 (1)	9 (7)
30–39	0	1 (1)	0	1 (1)
Total	21 (8)	12 (3)	20 (7)	53 (18)

The figures in brackets refer to the number of cases in which there was another (possibly primary) cause of haemorrhage apart from anticoagulant therapy

It should be pointed out here that a severe loss of blood in itself may cause a fall in the PP value supposedly partly as a result of loss of plasma and therefore

of prothrombin and proconvertin and partly as a result of reduced tolerance to dicoumarol because of poor general condition (possibly shock) There is thus reason to believe that the PP value recorded once haemorrhage has started is not infrequently lower than that present when the haemorrhage began

A couple of cases in this investigation seem to corroborate this suggestion

A 52 year old man noticed just before he attended the clinic that his stools had become black but he did not mention this to the author His PP value was stable between 11 and 12 % and he continued with the same dose of dicoumarol Two days later he was admitted to hospital with melaena His PP value was then 5 % Hb 76 % He recovered rapidly after transfusion X ray showed a duodenal ulcer Thus in this case the bleeding started when the PP value was over 10 % but the value sank during the haemorrhage right down to 5 % in a couple of days

A 76 year old man who for over 4 years had had a very stable PP graph and tolerance to dicoumarol developed during ideal therapy (PP value approx 15 %) a significant hypochromic anaemia (Hb approx 50 %) On account of a misunderstanding he continued to take his normal dose of dicoumarol for 8 days after the anaemia was diagnosed while he was waiting to be admitted for further investigation On admission his haemoglobin was the same but his PP value had fallen to 3 % X ray showed gastric carcinoma and he was later operated on without complications *Thus* in this case as *well* the haemorrhage started while the PP value was in the therapeutic region but his tolerance to dicoumarol decreased so that it was dangerously low on admission

Haemorrhage in itself therefore seems to be able to increase the bleeding tendency already present when the bleeding starts This is of considerable practical interest It makes it clear that when one finds a low PP value in a case of severe haemorrhage one must not just accept that this low value is in itself either a satisfactory or the only explanation of the episode In all such cases one must investigate the patient thoroughly in case there is a local pathological process which is a contributory cause As we will see later it is not infrequent that such a process can be demonstrated Dicoumarol therapy thus sometimes makes an earlier diagnosis possible specially in urinary tract diseases and ulcer or cancer of the gastro intestinal tract

Haemorrhages with a contributory local cause

On clinical or radiological examination of many of the cases of haemorrhage in this investigation pathological changes were demonstrated that must be considered as contributory or possibly the primary cause of the haemorrhage The number of such cases is shown in brackets in *Tables 86 and 87* We will now look into these cases in more detail For the sake of brevity the PP values registered in connection with each episode have been noted in brackets without further designation

Trauma was the contributory cause of skin bleeding in 1 case (20 %) and of muscle haematoma in 1 case (8 %)

A varix in the nostril was shown after epistaxis in 2 cases (13 and 34 %) The bleeding stopped after cauterisation

Urolithiasis was the cause of mild haematuria in 6 cases (26 22 16 25 25 and 20 %) Five of these episodes were in one individual patient who during the treatment period passed renal calculi 5 times

Duodenal ulcer was demonstrated on X ray in 1 moderate (11 %) and 2 severe (5 and 5 %) cases of melaena Two of these three patients had previously had an ulcer and one of these had often had melaena

Gastritis was demonstrated on X ray in 1 case of melaena (7 %) in a 43 year old man who for several weeks had had anorexia wind heartburn and occasionally sudden vomiting He was given a blood transfusion but was not admitted to hospital Treatment was continued without further interruption and without any other complications

Pre pyloric gastritis and a small diaphragmatic hernia was demonstrated in one case of haematemesis (10 %) The patient was a 78 year old man who had no previous gastric history and who was admitted after an acute transitory haematemesis It happened on New Year s Eve after he had passed the last 7–8 hours of the old year by indulging in gastronomic and alcoholic excesses On reaching his home he was very excited by a man who tried to force his way into the house and the police had to be summoned The patient was admitted to hospital (Hb 95 %) and was given 1 litre blood The haemorrhage stopped at once and treatment was continued without further interruption after a slight reduction of the dose of dicoumarol

Gastric carcinoma occurred in one case of occult bleeding and progressive anaemia (15 %–3 %) See p 164

It is thus clear that in 6 of the 7 cases with haematemesis melaena or occult bleeding during treatment signs of gastric or duodenal disease were demonstrated

In the 7th case the conditions at the time of the haemorrhage were rather unusual and the case will therefore be summarized briefly The patient was a 62 year old man who had been in hospital for 2½ weeks with a serious intercurrent disease There were difficulties in feeding by mouth and dicoumarol had therefore to be stopped for 3–4 days When treatment was reinstituted in hospital his general condition was very poor and two weeks later his PP value fell from 26 % to 7 % in 2 days In connection with this the patient had a large haematemesis and melaena which persisted for the next 3 days He had to have 4 5 litres of blood On the day after the haemorrhage the PP value was 13 % and the next day it was 60 % In the years 1934–1937 the patient had often had a pyloric ulcer with severe melaena but he had been free from haemorrhage since a partial gastrectomy in 1937 When the present episode occurred he had been getting stable and ideal treatment with dicoumarol as an out patient for 45 months The

patient was very troubled by angina pectoris and did not want a radiological examination Dicoumarol was stopped (It should be mentioned here that duodenal ulcer without any sign of bleeding was demonstrated radiologically in 2 patients of whom one had previously had an ulcer In both these cases adequate anticoagulant therapy was continued while the ulcers healed There were no complications)

Haemorrhoids were present in 1 case with mild rectal bleeding (11 %)

Cerebral tumour (glioblastoma in the left temporo occipital region) was shown at autopsy in 1 case who 3–4 months earlier had been admitted for subarachnoid haemorrhage when the treatment was adequate (24 %)

There were 4 cases of *cerebral haemorrhage* In all the cases the outcome was *fatal* and the diagnosis was verified at autopsy Three of the cases (1 man of 67 and 2 women of 67 and 76) had fixed hypertension average blood pressure 190/110 210/105 and 185/105 mm Hg respectively When the haemorrhage occurred the PP values were 14 11 and 7 % respectively

The fourth patient who died of cerebral haemorrhage was a 61 year old man with diabetes mellitus and severe generalised arteriosclerosis He had been treated for obliterating arteriosclerosis and had al o had signs of a cerebral vascular accident with transitory right sided hemiparesis and persisting mental deterioration and retardation before the infarct His PP graph had been satisfactory at regular clinics every 2–3 weeks While he was on holiday he was not able to attend the clinic He was told over the telephone that he should continue with the same dose of dicoumarol for a few days but that he should come to a clinic as soon as possible On arrival at the hospital by ambulance 5 days later he was comatose with signs of a large cerebral haemorrhage His PP value was 3–4 % He died shortly afterwards (The occurrence of cerebral vascular accidents in the control group will be discussed later)

If when calculating the incidence of haemorrhagic complications in this investigation all episodes where the author was able to demonstrate a contributory local cause are excluded there are 22 moderate or severe haemorrhages in a total of 418 3 years of treatment (all the cases of cerebral haemorrhage are included) This gives one moderate or severe haemorrhage every 19 years of treatment per patient

Waaler (1956) finds also after exclusion of the cases in which a contributory local cause could be demonstrated 25 haemorrhages in 670 years of treatment This gives approximately one haemorrhage every 27 years of treatment per patient

Treatment of the haemorrhagic complications

Although the treatment of the haemorrhagic complications has been touched on above a brief supplementary account is needed

The first point is that in none of the cases was there really serious dicoumarol intoxication leading to failure of coagulation and difficulty in management There

were thus no cases in which there was bleeding from several places at once And in all the cases with one exception the PP value rose to the therapeutic region (10–30 %) or even higher on the day after the haemorrhage (after stopping the dicoumarol and sometimes injecting vitamin K (menadione) and/or blood transfusion) Subsequently the PP value rose rapidly without further treatment The most serious dicoumarol intoxication was observed in a 67 year old man with hypertension who had had a very stable PP graph (16–26 %) for several months He was not able to attend the clinic as he was in bed at home with pneumonia being treated by another doctor Ten days later he was admitted to hospital with massive haematuria His PP value was 1 % He was given ½ litre blood and 100 mg menadione i v The next morning his PP value was 9 % and the day after 22 % The haematuria disappeared in 3 days and the treatment with dicoumarol was then continued without interruption

Of the 20 severe haemorrhages there were *8 cases who received blood transfusions* As mentioned earlier none of the cases of mild or moderate haemorrhage were treated in this way

Of the total 53 recorded cases of haemorrhage there were 17 who were treated with vitamin K (menadione) 50 mg (or 100 mg) i v Synthetic vitamin K_1 (Konakion Roche) 10 mg orally was only given in a couple of cases

At first intravenous injection of 50 mg menadione was given to a few cases if the PP value was low even if no bleeding occurred Later on this was not done the dose of dicoumarol was merely withheld for 1–3 days depending on the PP value and the tolerance Experience has shown that in patients who have a high tolerance to dicoumarol the PP value rises faster and more easily out of the danger zone than it does in patients who have a low tolerance While in the former cases it is sufficient to reduce or withhold the dose for one day in the latter it is often necessary to withhold the dose for several days before the PP value rises from e g 5–6 % to over 10 %

Haemorrhagic complications in the control group

Before finishing the discussion of the haemorrhagic complications we must mention the incidence of haemorrhage in the control group

First of all it must be mentioned that in the large number of interviews with the patients in the control group the author did not inquire especially into the past history in order to record the occurrence of mild insignificant haemorrhages Further these patients were not especially warned to look out for such episodes or to inform the author as the patients in the treated group did

A fair comparison can therefore only be made of the haemorrhages that were of such a type or such severity that treatment was required On account of the constant contact with all the patients and the thorough examination of the case histories each time they were admitted the author believes that he got to know about all the moderate or severe cases of haemorrhage in the control group

The following cases were observed

Epistaxis	2 cases
Haematuria (prostatic adenoma)	1 case
Haemoptysis (pulmonary embolism)	1 case
Cerebral haemorrhage	5 cases of which 1 was fatal

The fatal case of cerebral haemorrhage who died in a few hours was a 64 year old woman with fixed hypertension average BP 200/120 The haemorrhage was confirmed at autopsy Three of the 4 non fatal cases all women aged 59 57 and 54 years also had fixed hypertension Their average blood pressures were 180/105 210/120 and 230/125 respectively Two of them developed severe persistent hemiparesis and were completely invalided The third also had a significant paresis but it regressed leaving only moderate sequelae Haemorrhage was considered to be the most likely cause of these 3 cases but thrombosis or embolism cannot be excluded The last cerebral vascular accident occurred in a 55 year old man with normal blood pressure He developed a sudden progressive total paralysis on the left side which persisted so that he was completely invalided He died 9 months later At autopsy a large old area of cerebral softening was found involving the right frontal lobe the tip of the temporal lobe the lenticular nucleus and internal capsule The pathologist was not certain whether the cause had been haemorrhage or thrombosis

Thus in the control group there were 1 certain 3 probable and 1 possible cases of cerebral haemorrhage of which 4 were very serious and one of these fatal

It should be noticed that the number of cerebral vascular accidents in the control group exceeds that in the treated group But while the 4 cases in the treated group were fatal immediately only 1 of the 5 episodes in the control group was fatal It is certain that anticoagulant therapy in such cases contributes to a massive haemorrhage This was demonstrated by the post mortem findings in the 4 treated cases discussed (see p 187) Fixed hypertension (and also significant cerebral arteriosclerosis) must therefore be regarded as relative contraindications to long term anticoagulant therapy This has also been mentioned by others It should be remembered here that most of the fatal cases of haemorrhage during long term therapy were cases of cerebral haemorrhage

If we now exclude all cerebral vascular accidents in both groups we find only 4 moderate haemorrhages (epistaxis haematuria and haemoptysis) in the control group against a total of 28 moderate or severe cases in the treated group Although in many of the haemorrhages in the treated group contributory causes apart from anticoagulant therapy were found it must be concluded that treatment with dicoumarol has been the most important factor in the pathogenesis of the haemorrhages in most cases It is very probable that the same is true of the mild cases

Summary and conclusion

In this chapter the haemorrhagic complications during treatment with dicoumarol have been discussed—the number of cases the type and degree of severity Further the PP values recorded in connection with the haemorrhages are mentioned It has been shown that the PP value was less than 10 % in about half the recorded cases while in the other half it varied between 10 and 34 % In a good ⅓ of the cases contributory causes apart from anticoagulant therapy were found There were 4 cases of cerebral haemorrhage all of which were fatal The number of serious cerebral accidents in the control group was similar i e 5 cases Only 1 was fatal but 3 resulted in permanent invaliding Excluding the cerebral accidents in both groups there were only 4 haemorrhages of clinical significance in the control group against 28 in the treated group This shows that in most cases anticoagulant therapy must be reckoned as the most important pathogenic factor in these haemorrhages (even if there is another contributory cause)

The incidence of haemorrhagic complications during anticoagulant therapy should be seen in relation to the antithrombotic effect achieved in the period of treatment This information is only given exceptionally in previously published articles In spite of the treatment being very intensive in this investigation (see Chapter IX) the incidence of haemorrhagic complications is no higher than in previous investigations by other workers in this field

CHAPTER XIV

Investigation of liver function during long term treatment with dicoumarol

The question of whether or not dicoumarol damages parenchymatous organs has attracted attention since this drug was brought into use as an anticoagulant *Bingham Meyer and Pohle* (1941) gave repeated large doses and enormous single lethal doses to dogs without being able to demonstrate any morphological signs of damage in parenchymatous organs Nor could they show changes in the liver function tests in dogs or men treated with dicoumarol Similar experiments have been carried out by *Butt Allen and Bollmann* (1941) and others with the same result

Liver function tests and post mortem examinations of the liver after administration of dicoumarol for many years have also shown no sign of toxic damage (see *Nichol and Fassett* 1947 *Foley and Wright* 1949 *Nichol and Borg* 1950 *Nichol Phillips and Jenkins* 1954 and others)

In the present investigation the following liver function tests were carried out in the patients in the treated group (1) icterus index (2) thymol turbidity (3) Gros test and (4) fractional estimation of serum albumin and serum globulin (For technique see p 52)

These tests were carried out once or several times in all 119 patients except in 3 who died early in the observation period In 88 cases the tests were done shortly before or shortly after the beginning of the observation period In 16 of these cases who died the tests were not repeated later In the remaining 72 cases the tests were repeated before the end of the observation period In 28 cases the liver function tests were done for the first time after a year or two of dicoumarol therapy All these tests were normal and were therefore not repeated later

In 3 cases the thymol turbidity test was positive at the beginning of the observation period and remained positive when tested later One of these patients had persistent hepato and splenomegaly of unknown aetiology Another was an alcoholic and had rheumatoid arthritis and a constantly raised BSR The third case had moderate hepatomegaly after living in the tropics for many years She had had repeated attacks of malaria once with protracted jaundice

In 2 cases the thymol turbidity test was positive at the beginning of the observation period but later became negative One of these patients had had acute hepatitis but in the other the reason was unknown

In 5 patients the thymol turbidity test was negative at the beginning of the observation period but later became positive In 1 of these cases the probable reason was heart failure but in the other 4 cases no special reason could be found

Otherwise all the liver function tests were completely normal in all cases It is therefore unlikely that the positive thymol turbidity test in the 4 patients mentioned was due to treatment with dicoumarol although this possibility cannot be excluded This test can become positive in many different conditions and can therefore not be taken as an indication of liver damage without more ado

Summary and conclusion

In this chapter an account has been given of the investigations carried out to test the liver function during long term treatment with dicoumarol With the tests used there was no definite evidence that this form of treatment damages the liver function The thymol turbidity test did however become positive during the observation period in 4 patients for undiscovered reasons

CHAPTER XX

Supplementary comparison of the treated and control groups during observation period Mode of life and morbidity

In this chapter an account will be given both of some aspects of the patients mode of life including personal habits and ability to work and of the morbidity during the observation period It is intended as a supplement to the previous comparison of the treated and control groups (see Chapters X and XI)

The nature of the present problem made it important to put a great deal of weight on making certain that both groups had uniform treatment apart from the use of anticoagulants This has been discussed in detail in Chapter VIII If indicated normal cardiological treatment was always given to the patients in both groups On the other hand efforts were made to avoid all special and unnecessary additional treatment which might influence the results

Diet alcohol tobacco

A detailed investigation of the diet alcohol and tobacco habits of the patients was not attempted In the many conversations with the patients however the author got a fairly good picture of such personal habits

No special instructions were issued about *diet* The patients were told to avoid putting on weight Weighing the patients before the end of the observation period showed that in most cases the weight had remained practically unchanged Considerable loss of weight was however observed in some patients in both groups who developed terminal cachexia Obese patients were generally advised to lose weight but no special instructions were issued for dietetic or other treatment of obesity One woman in the treated group who was very obese lost about 20 kg on her own initiative All the other very obese patients remained obese Neither low cholesterol nor low fat diets were recommended to any of the patients If the patients inquired especially the author replied that the significance of cholesterol in coronary sclerosis is not yet sufficiently clear and that it is not yet known which diet is the most suitable On the whole it can be said that the patients in this investigation stuck to their normal diets (Salt restriction in cases of heart failure was naturally an exception)

Many patients asked whether *alcohol* was permitted It was not prohibited but patients were warned against excess and it was stressed that in coronary disease alcohol should only be taken when at rest A couple of patients in each group who were alcoholics were advised to stop or drastically reduce their intake but this advice had no effect In a few cases where knowledge of the patients made misuse of alcohol unlikely alcohol was recommended to assist relaxation and sleep in the evenings Exceptionally alcohol was also tried for angina pectoris None of the patients became alcoholics during the observation period and most of them seemed only to take a very moderate amount

Many patients also asked about the use of *tobacco* The author replied that the significance of tobacco in coronary disease is not yet clear No patients were forbidden to smoke Some heavy smokers were advised to cut down but the advice was only seldom or temporarily taken Some moderately heavy smokers in both groups cut down on their smoking but only 3 patients in the treated and 5 in the control group completely stopped smoking after their infarct Most patients seemed to smoke as before and some smoked more than before

Ability to work and type of work

The author knew the type of work and the patients ability to work in all cases A general picture of these conditions is given in *Table 88* The patients have been divided roughly into 3 groups according to type of work (1) manual labour (i e heavy or light) (2) not manual labour (usually office work administrative work non strenuous shop work) and (3) domestic work Temporary interruptions because of illness during the observation period are not shown in the table

The table shows that the number of patients who returned to their previous work and were still working at the end of the observation period was somewhat larger in the treated than in the control group However the difference is small and seems to depend partly on the fact that a few more of the patients in the control group had reached retiring age and stopped work before the original acute infarct Otherwise the difference between the groups is strikingly small and hardly gives reason to believe that the treatment has influenced the patients ability to work On the other hand the table provides good evidence of the comparability of the two groups and of the fact that they have been treated in the same way as regards returning to work after the acute infarct

Frequency and duration of admissions to hospital

The author knew all the details of all the admissions to hospital for the patients in this investigation during the observation period The case histories covering these admissions were always studied carefully and a summary included in the author s file It is of interest to examine morbidity by comparing the frequency

TABLE 88

The patients' ability to work and type of work in the observation period

		Manual labour Trial	Manual labour Control	Non-manual labour Trial	Non-manual labour Control	Domestic work Trial	Domestic work Control	All types of work Trial	All types of work Control
Stopped work because	(1) retired	3 (1)	11 (6)	3	4 (2)	1		7 (1)	15 (8)
	(2) illness	6 (2)	5 (4)	2 (2)	1			8 (4)	6 (4)
Did not return to work because	(1) retired	1	1					1	1
	(2) illness	5 (3)	6 (4)	2 (2)	1 (1)	1	1 (1)	8 (5)	8 (6)
	(3) early death	3 (3)	5 (5)	1 (1)	1 (1)	1 (1)	1 (1)	5 (5)	7 (7)
Returned to previous work	(1) continued working	26	19	30	23	10	7	66	49
	(2) stopped working								
	(a) retired			2	2			2	2
	(b) illness or death	6 (3)	5 (2)	3 (2)	8 (7)	1 (1)	2	10 (6)	15 (9)
Started lighter work	(1) continued working	1	2	1		5	4	7	6
	(2) stopped working								
	(a) retired			1				1	
	(b) illness or death	2 (1)	4 (3)		1 (1)	2 (2)	4 (4)	4 (3)	9 (8)
Total		53 (13)	58 (24)	45 (7)	41 (12)	21 (4)	19 (6)	119 (24)	118 (42)

The figures in brackets refer to the number of deaths in each group

and duration of the admissions to hospital in the treated and control groups. It is of special interest to compare the admissions for cardiovascular diseases. Cardiovascular and non-cardiovascular diseases (intercurrent diseases) will therefore be considered separately.

TABLE 89

Admissions to hospital during observation period

	Total observation period (months)	Total number of cases with new admission	Hospitalisation for cardiovascular disease: No. cases	No. adm.	Total duration (months)	Hospitalisation for intercurrent disease: No. cases	No. adm.	Total duration (months)
Treated group (119 cases)	5020	56	44	81	61	29	51	25
Control group (118 cases)	4326	73	64	114	90	22	44	27

Table 89 gives a general picture of the admissions to hospital during the observation period. The number of patients in each group that had one or several new admissions to hospital is shown. Further the number of patients, number of admissions and total duration of the new admissions for cardiovascular diseases and intercurrent diseases in the two groups are indicated. It should be mentioned that hospitalisation of patients in the treated group with haemorrhagic complications has been included under cardiovascular diseases.

The table shows that there were more hospitalised patients and the number was considerably larger and the total duration longer of the admissions for cardiovascular diseases in the control than in the treated group. These data provide a very convincing supplement and support for the data in the comparison of the recurrent infarcts and mortality (see Chapters X and XI).

It is also seen that the number of hospitalised patients and the number of admissions for intercurrent diseases were slightly larger in the treated than in the control group, as one would expect considering the difference in length of the observation period. The total duration of these admissions was, however, slightly longer in the control than in the treated group. This was because 3 patients in this group were in hospital for relatively long periods with myelomatosis, malignant cylindroma in the trachea and sciatica respectively.

Heart failure

Many patients were treated for heart failure during the observation period. Heart failure was taken to include left heart failure with dyspnoea at rest, especially nocturnal dyspnoea, and right heart failure with peripheral oedema. Dyspnoea on exertion, which is often very difficult to assess, was not included.

Table 90 gives a general picture of the distribution of the cases with heart failure. It shows the number of patients in the treated and control groups with (1) severe progressive heart failure, (2) moderate, sometimes temporary, heart failure compensated by treatment and (3) no sign of heart failure. Some patients died so early in the observation period that their condition was impossible to assess. The number of such cases is given at the bottom of the table.

TABLE 90

Heart failure during observation period

Degree of heart failure	Treated group No. cases	Control group No. cases
Severe, permanently progressive	4	12
Moderate, sometimes temporary comp. by treatment	16	17
No sign of failure	94	80
Uncertain	5	9
Total	119	118

Heart failure in coronary disease is related to the degree of myocardial damage, which usually depends on the size and number of infarcts. The table shows that there were 3 times as many cases with severe, permanently progressive heart failure in the control as in the treated group, i. e. 12 and 4 cases respectively. This is reasonable because of the considerable difference in incidence of recurrent infarction in the two groups (see Chapter X). Otherwise there is no obvious difference between the groups.

It should be mentioned here that 26 patients in the treated and 34 in the control group received digitalis continuously. As well as for definite cases of heart failure, digitalis was sometimes tried for dyspnoea on exertion and exceptionally for cases of angina pectoris with latent heart failure as a possible contributory cause.

Angina pectoris

A detailed investigation of whether long term treatment with dicoumarol in myocardial infarction has any effect on the tendency to angina pectoris is outside the scope of this study. No attempt was therefore made to make a regular and detailed investigation into the degree of angina pectoris either by careful past history, assessment of the effort tolerance or with the help of graded exercises or an anoxaemia test. Such investigations in a heterogenous group of patients such as the present one would be extremely difficult both to carry out and assess. The patients were of all ages though the average age was fairly high and there was a relatively high incidence of general physical infirmity. Their modes of life differed greatly, so did their ability to work and their type of work, and there were large differences in cardiac status. Graded exercises and especially an anox-

angina test would often have been contraindicated on account of a not inconsiderable risk

Any assessment of prophylactic therapy in angina pectoris is very difficult One source of error will be emphasised namely that cases of angina pectoris often have spontaneous natural fluctuations Relatively good periods or periods with improvement are not infrequently followed after intervals varying up to a year by periods of definite deterioration (see e g *Boas* 1951) *Waaler* (1956) has recently given an excellent survey of this and other sources of error in the assessment According to him an ideal investigation should fulfill the following conditions (1) A selection of patients in whom coronary sclerosis is the only or the most important cause of the disease (2) Large number of patients (3) Long observation period (4) Placebo treated control group (5) Double blind technique In addition to these there is perhaps the additional question of an objective method for assessing the effort tolerance

The present study only fulfills the first three conditions It was however possible to compare a treated with an untreated group of patients therefore although placebos were not used a rough comparison of angina pectoris in the two groups may be of interest

All the patients in this study were examined clinically for angina pectoris They were all asked about the frequency of the attacks and their immediate cause and at each follow up clinic whether their condition had improved or deteriorated The investigator was especially aware of the fact that some patients confuse angina pectoris with dyspnoea on exertion and he questioned all the patients thoroughly with this in mind It is therefore unlikely that errors arose in this differential diagnosis

On the basis of the information received the patients were divided into 4 groups

(1) *Severe invaliding angina pectoris* This group included patients who throughout the whole period of observation had very low effort tolerance and frequent severe attacks usually several times a day Most of the patients in this group also had occasional attacks when at rest

(2) *Moderate angina pectoris* This group included patients who throughout the whole period of observation had typical angina of effort usually with daily attacks occurring on normal everyday exertion i e on going up stairs etc These patients had no attacks of pain at rest and got on fairly well once they had learned to slow down

(3) *Mild angina pectoris* This group included patients with less frequent more irregular attacks of angina pectoris The attacks usually occurred however when the patients forgot to be careful of their heart The attacks were usually brought on by unusual occurrences such as emotional upset physical exertion on a full stomach walking in severe cold etc

(4) *No angina pectoris*

TABLE 91

Angina pectoris during observation period

	Treated group	Control group
Severe angina pectoris	9 (4)	13 (9)
Moderate angina pectoris	24 (6)	23 (7)
Mild angina pectoris	35 (4)	39 (8)
No angina pectoris	46 (5)	34 (9)
Uncertain (short observation period)	5 (5)	9 (9)
Total number of cases	119 (24)	118 (42)

The figures in brackets refer to the number of deaths during the observation period

Table 91 shows the distribution in the different categories of angina pectoris of the patients in the two groups It is evident that there is very little difference between the treated and control groups The treated group is slightly better off but it should be remembered that this may be explained by the fact that there were fewer recurrent infarcts in this group

None of the patients in group 1 either in the treated or the control group showed any tendency to improve The course of the disease for patients in group 2 and especially in group 3 was more variable Periods of improvement were observed among these patients in both groups Periods with marked deterioration also occurred even in a not inconsiderable number of patients in the treated group

This comparison has too many sources of error to give a dependable evaluation of the effect of this prophylactic therapy in angina pectoris The author has not however been convinced that long term treatment with dicoumarol has any *definite* prophylactic effect against the tendency to attacks of retrosternal pain in this group of patients

Increase in size of the heart

In most of the patients in this study radiological examination with estimation of the cardiac volume was carried out at the beginning of the observation period (See pp 84–86 and Tables 40 and 41) During the observation period in many cases radiological measurements were taken several times usually during new admissions In the patients who lived to the end of the observation period the measurements were repeated towards the end of the period The same technique was used for all the radiological investigations and the measurements were all made by one individual (see Chapter IV p 53)

A comparison of the alterations in cardiac volume noted during the observation period from patient to patient and from group to group is difficult to make accurately because of the very variable intervals between examinations The

considerable differences in the length of the observation period was one of the most important reasons for this. In order to obtain as accurate a picture as possible of the alterations in cardiac volume in relation to the values found at the beginning of the observation period the following method was adopted: with the original volume as the origin the changes in volume in each individual patient were entered on separate sheets of graph paper for the treated group and control group. The interval between measurements (in months) was taken as the abscissa and the difference in cardiac volume (in ml/sq. metre body surface area) as the ordinate. In the cases in which only one measurement was taken before the end of the observation period this value was entered as a point on the graph paper. In the cases in which several measurements were taken the points were joined together by lines. The two diagrams gave a visual impression of the alterations in cardiac volume and showed immediately that there was no obvious difference between the treated and control groups. A more detailed statistical comparison was therefore not carried out. The diagrams are omitted to save space.

Finally, it must be mentioned that a moderate increase in the relative cardiac volumes of 50–90 ml/square metre body surface area was found in 18 cases in the treated and 16 in the control group. A definite and considerable increase in volume of 100 ml/square metre or more was found in 9 cases in the treated and 14 in the control group.

Electrocardiographic investigation

In this study electrocardiograms were taken regularly 2–4 times a year, somewhat more frequently in the control than in the treated group. In addition supplementary electrocardiograms were taken after a suspected attack of pain or when arrhythmia or tachycardia was found on clinical examination. (Extrasystoles were often heard on auscultation but electrocardiograms were not taken in such cases unless the diagnosis was uncertain and the existence of other forms of arrhythmia was suspected.) Finally, many electrocardiograms were taken during admissions to hospital in the observation period, especially to verify the diagnosis of new infarcts.

The electrocardiographic findings will not be analysed in detail, but it is of interest to make some comparisons between the treated and control groups. The electrocardiograms in both groups were therefore studied for the following conditions:

(1) *Tendency to return to normal*: the number of patients in each group was counted in which the electrocardiograms returned to normal either temporarily or for the rest of the observation period. Left axis deviation was here taken as normal and most weight was put on the ST and T changes returning to normal.

(2) *Occurrence of arrhythmia*: (a) paroxysmal or permanent atrial fibrillation (or flutter), (b) paroxysmal tachycardia.

(3) *Occurrence of block* (a) A–V block grades II and III (b) bundle branch block (A–V block grade I was not included as it is so often the result of treatment with digitalis)

Table 92 shows the result of the analysis of these phenomena The table shows that a lasting return to normal of the electrocardiogram was observed in 28 patients in the treated and 17 in the control group This difference might indicate that long term treatment with dicoumarol favours the tendency for collateral vessel formation and recanalisation in coronary occlusion Otherwise there is no obvious difference between the groups

TABLE 92

Electrocardiographic findings

ECG findings			Treated group (119 cases)	Control group (118 cases)
Return to normal	Lasting		28	17
	Temporary		10	12
Arrhythmia	Atrial fibrillation	Paroxysmal	4	3
	(or flutter)	Permanent	1	2
	Paroxysmal tachycardia		2	3
Block	A–V block grades II and III		1	4
	Bundle branch block		2	2

Attention should perhaps be drawn to the strikingly low frequency of atrial fibrillation especially when permanent in spite of the fact that all the patients in this investigation had had one or several definite infarcts Paroxysmal tachycardia was also seldom observed in the treated group there was 1 case of supraventricular and 1 case of ventricular tachycardia and in the control group 3 cases of ventricular tachycardia A considerable proportion of the cases of arrhythmia and heart block developed in connection with new infarcts

Extra cardiac thromboembolic complications

Intermittent claudication

Finally it is of interest to mention that during the observation period intermittent claudication developed in 8 patients in the control group and only 1 in the treated group None of these patients had had this symptom before the recorded acute infarct This difference might be interpreted as indicating that continuous treatment with dicoumarol has a prophylactic effect on the development of secondary thrombosis which is often assumed to be the direct cause of the clinical symptoms in obliterating arteriosclerosis (see also Chapter VI p 67)

Other extra cardiac complications

Apart from the possible arterial thromboses mentioned above extra cardiac thromboembolic complications were extremely rare No such complications were observed in the treated group and only 2 cases in the control group (pulmonary embolism and thrombophlebitis)

Summary and conclusion

In this chapter an account has been given of the mode of life of the patients and the morbidity during the observation period Special restrictions concerning diet (calorie and cholesterol intake) alcohol and tobacco were not issued to patients in either the treated or control group There was also no obvious difference between the groups as regards ability to work and type of work (see Table 88) The frequency was considerably higher and the duration longer of admissions to hospital for cardiovascular diseases during the observation period for the patients in the control than in the treated group but there was no difference between the groups as regards morbidity from intercurrent diseases (see Table 89) Severe progressive heart failure was observed in 3 times as many patients in the control as in the treated group 12 and 4 cases respectively (see Table 90) A detailed investigation was not made into the prophylactic effect of treatment on angina pectoris but a rough comparison was made of the two groups and there was no obvious difference (see Table 91) An analysis of the radiological changes in cardiac volume during the observation period also showed no obvious difference between the groups A considerable increase in the relative cardiac volume was observed in about 10 % of the patients The large number of electrocardiograms recorded during the observation period showed that a lasting return to normal after the recorded infarct was observed in considerably more cases in the treated than in the control group (see Table 92) Permanent atrial fibrillation was only observed in 3 cases 1 in the treated and 2 in the control group Intermittent claudication developed during the observation period in 8 patients in the control and 1 in the treated group who had not previously had this symptom Other extra cardiac thromboembolic complications were extremely rare

CHAPTER XXI

Medical and psychological significance of regular supervision of patients after myocardial infarction

In spite of an increasingly optimistic view of the prognosis it is well known and generally known that after an acute myocardial infarct patients are apt to have an uncertain future This is seen very clearly in this study in the different fates of the patients during the observation period especially as shown in Chapters X XI and XX

Popular medical articles in the daily press and talks on the radio have recently given the general public increasing knowledge about diseases and their prognosis It is a matter of opinion whether this is a good or a bad thing Certainly for all thinking people the development of a myocardial infarct is not only a physical but also a considerable emotional trauma which makes the future uncertain and insecure In most of the uncomplicated cases the patient gradually more or less completely regains his confidence and faith in life In some more sensitive patients the knowledge of the uncertain prognosis brings a permanent either manifest or latent feeling of insecurity and fear which is often kept going by the subsequent course of the disease Angina pectoris unexpected attacks of coronary insufficiency or more atypical cardiac pain anterior chest wall syndrome palpitations infra mammary pain etc often darken the existence of patients with coronary diseas

Regular supervision and possible treatment of patients after myocardial infarction therefore has a double significance (1) to supervise the condition of the heart and to institute the necessary cardiological treatment if new symptoms develop and (2) by doing this to be able to console the patient and reassure him that after thorough examination either it has been found that his condition is satisfactory or that treatment is necessary for the symptoms that have worried him

It has been said that the regular venepunctures during long term anticoagulant therapy contribute to making and keeping a cardiac neurosis going In the author s experience this only occurs very exceptionally On the contrary the regular clinics and contact with the patients provide a possibility for cardiological and psychological supervision and treatment which in most patients seems to give security and confidence However it is undoubtedly of utmost importance that the physician in charge of the anticoagulant therapy is also willing and able

to take complete responsibility for all aspects of the heart disease In the author s opinion ideally one should not emphasise long term treatment too much when it is instituted It should not become the sole focus of the patient s attention but as far as possible merely an item amongst the rest of the treatment

The fact that after myocardial infarction patients feel a need for the security of regular supervision and observation by a doctor has in the present study been most clearly shown in the *control group* Almost without exception these patients have for 3–6 years attended clinics regularly 3–4 times a year on the exact date and hour arranged 3–4 months beforehand They also contacted the investigator if they had unexpected developments or worries In the author's opinion this need of patients with coronary disease for regular and competent supervision and treatment has not previously attracted enough attention at any rate in this country

CHAPTER XVII

Autopsy findings

Autopsy was carried out in a relatively large number of the cases in this investigation who died during the period of observation An account will now be given of the most important findings

Autopsy findings are especially interesting in an investigation into the effect of long term anticoagulant therapy after myocardial infarction for the following main reasons (1) To make certain that the original diagnosis of acute infarction was correct (2) To verify or discover the cause of death The most important point being to see whether it was cardiovascular or not if so to see whether the patient died of a new myocardial infarct or of some other cardiovascular condition (3) To verify the existence of clinically diagnosed or to demonstrate undiagnosed thromboembolic phenomena (4) To verify or demonstrate the existence of haemorrhages

The post mortems in this investigation were carried out following the routine normally used in the Department of Pathology in Ulleval Hospital Post mortems were thus not planned or carried out with this investigation especially in mind It was impossible to carry out more specialised scientifically planned post mortems because of pressure of work and frequently changing staff in the Department of Pathology

Number and distribution of post mortems Technique

Of the 66 cases who died during the observation period 43 had post mortems i e 19 in the treated and 24 in the control group In 4 of these cases of whom 3 died outside hospital and 1 in hospital post mortem was carried out on the initiative of the author and it was only possible for a partial autopsy with macro and microscopic examination of the heart In the other 39 cases a complete post mortem was carried out with examination of all the visceral organs including the heart and large blood vessels In 30 cases the brain was also examined

Macroscopic investigations In all the cases the heart musculature was examined relatively accurately and thoroughly Systematic macroscopic examination of the coronary arteries was also carried out partly by inspecting cross sections of the arteries and partly by opening up the arteries longitudinally Usually both methods were combined Further a systematic macroscopic hunt for mural thrombi on the endocardium was carried out Finally the main branches of the pulmonary arteries and the lungs were inspected for thrombo i

embolism and pulmonary infarction in all the cases except for the 4 partial autopsies

A systematic investigation of the visceral and peripheral arteries was however not carried out except in a few cases with clinically demonstrable thromboembolic phenomena Similarly the venous system was not examined for thrombosis

Microscopic investigations The heart was examined microscopically in 36 cases including the 4 partial autopsies In the 32 complete autopsies the lungs liver kidneys and sometimes other visceral organs were usually examined microscopically The brain was also examined microscopically in the majority of the 30 cases in which it was removed

Routinely microscopic investigation of the heart only included examination of sections from the cardiac musculature Usually histological examination of the coronary vessels was not carried out However this was done in some cases at the author s special request in order to verify the presence of suspected or definite macroscopic coronary thrombosis and to give some indication of the age of the thrombosis Mural thrombi on the endocardium were also examined microscopically in some cases

While the demonstration of an old fibrotic infarct in the cardiac muscle is usually easy it is sometimes more difficult to demonstrate a fresh myocardial infarct at autopsy In cases where death occurred minutes or a few hours after the beginning of an attack the pathological changes in the myocardium will either not develop or be very small In such cases the demonstration of fresh thrombotic (or haemorrhagic) coronary occlusion is the only pathological way of verifying the diagnosis These difficulties become even more pronounced if one is attempting to demonstrate a new infarct in a myocardium which is already altered by previous infarct(s) It is especially difficult to differentiate a new extension of a previous infarct if the interval between the two episodes is short These difficulties however only played a small part in this investigation apart from a few cases who died very early in the observation period

Finally it must be mentioned that although the autopsies were carried out according to routine the pathologist had read the case histories and therefore his main interest was in the cardiovascular system In most cases the author was also able to be present at the post mortems and to ask questions of special interest The significance of the question of thromboembolic phenomena was always especially pointed out to the pathologist The microscopic sections were also later gone through by Dr K Larsen from the Department of Pathology and the author

Characteristics of post mortem cases

Table 93 shows the ages and sexes of the post mortem cases It is evident that a relatively larger number of women in the treated group than in the control group had post mortems Further most of the autopsy cases in the control group

were relatively young Half the patients in this group were under 60 years old as against barely 1/3 of the patients in the treated group

Looking at the past histories it was found that 25 of the 43 post mortem cases had signs of coronary disease before the acute infarct that included them in the investigation i e 10 of 19 cases in the treated group and 15 of 24 in the control group

TABLE 93

Age and sex distribution of post mortem cases

Age Years	Treated group Men	Women	Control group Men	Women
40–49	0	0	1	0
50–59	4	2	10	1
60–69	6	5	7	2
70–75	1	1	2	1
Total	11	8	20	4

Post mortem verification of the original acute infarct

The diagnosis of the original acute infarct was confirmed in all post mortem cases Easily seen usually large fibrotic infarcts were found Their position was usually in good agreement with that found with the electrocardiogram In the 36 cases in which the heart musculature was examined microscopically there was also no doubt that the diagnosis had been correct In most cases fibrotic connective tissue with few cells was found in the old infarct areas In some cases where death occurred early in the observation period the microscopic changes were fresher with connective tissue containing more cells and blood vessels with pigmented macrophages and sometimes infiltration of lymphocytes and plasma cells In all cases the changes corresponded to the diagnosed age of the infarct

Causes of death

An account has previously been given of the causes of death in the patients in this investigation who died during the observation period (See Chapter X pp 140–143) Here therefore only the most important autopsy findings will be recapitulated and commented on briefly

Of the 43 post mortem cases a definite *non cardiovascular cause* of death was verified at autopsy in 3 cases There were two cases in the control group one who died of myelomatosis and the other of malignant cylindroma in the trachea with metastases The diagnosis had previously been made clinically in both these cases One patient in the treated group died of cerebral tumour histological diagnosis glioblastoma multiforme

In the other 40 post mortem cases the cause of death was *cardiovascular* *Cerebral haemorrhage* was verified as the cause of death in 5 of these cases 4 in the treated and 1 in the control group In 1 case in the treated group haemorrhage was found in both hemispheres breaking through into the ventricular system and bleeding in the base of the brain and round the medulla oblongata In the other 4 cases extensive bleeding was found in the internal capsule basal ganglia and the adjacent hemisphere on the same side breaking through into the ventricular system I eviously these cases and their relationship to treatment have been discussed in more detail (see Chapter XIII p 166) *Advanced generalised arteriosclerosis with secondary complications* was found in 4 case 2 in each group The post mortem findings in these cases have been discussed earlier (see Chapter XI p 142)

In the remaining 31 post mortem cases the cause of death was probably purely cardiac *Heart failure* was considered to be the cause of death in a 57 year old man who had had his first infarct 8 months before the one that included him in the investigation After a month of the observation period had elapsed he developed signs of severe left heart failure and shortly afterwards a rapidly progressive right heart failure with congestion of the liver and massive oedema In the weeks before death he was periodically confused and restless with Cheyne Stokes respiration and progressive uraemia Post mortem showed a considerably enlarged heart with extensive fibrotic infarction involving the whole anterior wall of the left ventricle which was very thin Further in this area there were macro and microscopic signs of relatively fresh pericarditis

Cardiac rupture with haematopericardium was found to be the cause of death in 2 cases both in the treated group One of these cases was a 64 year old man in whom the condition developed after 2 months observation i e 3 months after the original acute infarct The rupture was considered to be the result of a new infarct as the patient had had clinical signs of a new infarct with symptoms of shock 9 days before death At autopsy a considerably enlarged heart was found with aneurismal bulging of the lower half of the anterior wall of the left ventricle and an approximately 1 5 cm wide rupture in this area Further a relatively fresh thrombus was found in the first part of the descending branch of the left coronary artery with moderate histological signs of fresh infarction The other case of cardiac rupture occurred in a 61 year old woman who was still not discharged from the ward 53 days after the original infarct In this case autopsy showed an approximately 4 x 4 cm aneurism on the anterior wall of the left ventricle with rupture but no macro or microscopic signs of infarction There were signs of occluding atheroma in the descending branch of the left coronary artery and also in the right coronary artery but no sign of thrombosis

A clinical diagnosis of *perforation of the interventricular septum* was verified at autopsy in a 51 year old man in the control group after 23 days observation and about 2 months after the original acute infarct The lower 3 of the anterior

wall septum and apex of the left ventricle had been converted to a thin fibrous transparent membrane and there was an approximately 8 x 8 mm perforation in the septum partly covered by a thrombus

Sudden death probably caused by ventricular fibrillation or ventricular arrest occurred in 4 of the post mortem cases 3 in the treated and 1 in the control group Of the 3 patients in the treated group 2 had had a definite recurrent infarct earlier in the observation period At autopsy in all 4 cases extensive obliterating and sometimes occluding atherosclerosis was found in the coronary arteries and there were large advanced fibrotic infarction changes but no sign of coronary thrombosis or of fresh infarction

A new myocardial infarct was considered to be cause of death in the remaining 23 post mortem cases i e 6 in the treated and 17 in the control group New myocardial infarcts verified at autopsy included (1) Cases with macroscopic and/or microscopic signs of fresh infarction in the myocardium (2) Cases with macroscopic and sometimes microscopic signs of fresh coronary thrombosis but not always with simultaneous changes in the myocardium

Table 94 shows the cases in the treated and control groups in whom such changes were demonstrated The post mortem diagnosis is based on the pathological report on the macroscopic and sometimes microscopic findings together with a later inspection of the histological sections The pathological findings were moreover always compared with the clinical course of the disease the mode of death and the results of clinical and electrocardiographic investigations before death

TABLE 94

Post mortem verification of new infarction as the cause of death

Diagnosis verified	Treated group No cases	Control group No cases
Macro and microscopically	3	9
Only macroscopically	1	6
Only microscopically	1	1
Uncertain	1	1
Total	6	17

The table shows that the pathological diagnosis was uncertain in 2 cases In the case in the treated group death occurred in the course of a few minutes and no definite signs of a new infarct were found In the case in the control group the pathological description of the heart was so incomplete that no definite conclusions could be drawn Clinically the course of the disease definitely indicated that the cause of death had been a new infarct In addition to these cases of infarction there was also the case already mentioned in the treated group where

death occurred as a result of cardiac rupture and a case in the control group where death was primarily due to cerebral haemorrhage but where autopsy showed a new infarct as well

Thromboembolic phenomena

The distribution of the thromboembolic phenomena described in the pathological reports is shown in *Table 95* As mentioned the majority of the investigations were only macroscopic Any assessment of the age of a thrombus was therefore not very exact and was often not included in the description This means that the thrombi demonstrated in some of the cases who died early in the observation period may have been present before the beginning of the observation period possibly even as the cause of the original infarct On looking through the cases it was found that this was not possible in more than 3 cases 1 in the treated group and 2 in the control group On account of the relatively inaccurate routine method of investigation used the figures must be presented with reserve

TABLE 95

Thromboembolic phenomena demonstrated at autopsy

Type of thrombus	Treated group (19 cases) No cases	No sites	Control group (24 cases) No cases	No sites
Coronary thrombosis	5	6	14	17
Mural thrombosis	1	1	6	6
Peripheral arterial thrombosis	1	1	1	2
Cerebral thrombosis	0	0	1	1
Pulmonary embolism	0	0	1	?

The table shows that of the 19 cases in the treated group a thrombus in a coronary artery was demonstrated 6 times in 5 cases (26 %) One of these cases was a 74 year old woman who died of cerebral haemorrhage The haemorrhage occurred 11 days before death Dicoumarol was stopped at once she was given vitamin K and the PP value 9 days before death had risen to 52 % At autopsy a small non occluding mural thrombus was shown on an athero clerotic plaque in the right coronary artery Microscopy showed that the thrombus was quite fresh and had probably developed a few days before death after dicoumarol had been stopped

In the control group a thrombus in a coronary artery was demonstrated 17 times in 14 (58 %) of the post mortem cases The incidence of a thrombus as the cause of coronary occlusion is thus in the control group a little higher than the average incidence in previously published investigations of post mortem material (see p 16) This may indicate that the routine method used has in fact been relatively efficient in demonstrating thrombi in the coronary arteries

The table shows that *coronary thrombosis was demonstrated twice as frequently in the control as in the treated group* This difference in frequency is statistically significant The difference is even more marked if we exclude the above mentioned case in the treated group in which thrombosis developed after treatment had been stopped It must however be remembered that although the treated and control groups have been shown to be comparable when complete this has not been shown for the small number of post mortem cases in the two groups

Mural thrombosis in the left ventricle was demonstrated in 1 case in the treated and 6 in the control group

Sclerosis with thrombotic occlusion of the femoral artery was shown in one case in the treated group who died of generalised arteriosclerosis with complications Dicoumarol was stopped for the last 6–8 weeks before death on account of the rapidly progressive mental deterioration (See also p 142) In the control group arteriosclerosis with occluding thrombosis of the common iliac artery and gangrene of the toes was verified in one patient who also had thrombosis in one renal artery and pathological signs of cerebral thrombosis

Pulmonary embolism was shown at autopsy in a 72 year old man in the control group who had been in hospital for several months with heart failure after a recurrent infarct Autopsy also showed signs of a fresh myocardial infarct He had not received dicoumarol during the 3 weeks before death

The table shows that when all the thromboembolic phenomena found at autopsy are considered together they were almost 3 times as frequent in the control group as in the treated group The difference is even greater if one excludes the 2 cases in the treated group where thrombosis developed terminally after dicoumarol had been stopped The results of the post mortems may therefore indicate that long term treatment with dicoumarol has an antithrombotic effect and that this effect also includes coronary thrombosis It was however also shown that the treatment is not completely prophylactic in all cases On the whole the findings can be said to agree with the previously mentioned results of clinical observations

Haemorrhagic phenomena

The 5 fatal cerebral haemorrhages which were verified at autopsy have been mentioned earlier (see p 166 and p 187) In 2 patients in the treated group who both had hypertension and died of cerebral haemorrhage 1 and 2 pin point intimal haemorrhages respectively were shown in atherosclerotic plaques in the coronary arteries Only one of these haemorrhages had caused a bulging forward of the wall of the artery and slight narrowing of the lumen In the other two cases the arterial lumen was quite intact Neither secondary thrombosis nor occlusion was shown in either of these cases Apart from the haemorrhages mentioned here no sign of bleeding was shown at autopsy in the treated or control group

Cardiac hypertrophy Weight of heart

Before finishing this account of the autopsy findings an account will be given of the incidence of cardiac hypertrophy as judged by the weight of the heart in the post mortem cases In 34 cases the whole corpse was also weighed and in the other 9 cases the weight of the patient shortly before death was known

Table 96 shows the relationship between the weight of the heart in the post mortem cases and the standard values for the average cardiac weights in men and women of different body weights as given by *Smith* (1929) It is shown that the *weight of the heart was above the normal average values in all the cases and in* most cases it was considerably increased It is also seen that there is no noticeable difference between the treated and control groups in this respect

TABLE 96

Overweight of the heart in relation to Smith s average normal values

Overweight (grams)	Treated group No	Control group No cases
0– 74	2	1
75–149	2	3
150–224	4	9
225–299	5	7
300–374	4	2
375–	2	2
Total number of cases	19	24

Summary and conclusion

In this chapter an account has been given of the post mortem investigations in 43 of the total 66 deaths The autopsies were carried out according to routine and were not especially planned or executed with the problem of this study in mind In most cases however the author had the opportunity of seeing the autopsies and asking appropriate questions

The diagnosis of the original acute infarct was confirmed at autopsy in all the cases The autopsy findings are of especial value when considering the cause of death so the most important findings have been mentioned

Post mortem demonstration of thromboembolic phenomena is especially interesting Both coronary thrombosis and thromboembolism as a whole were *demonstrated 2—3 times as frequently* at post mortem in the control as in the treated group The number of cases with thrombosis shown at autopsy in a coronary artery is statistically significantly higher in the control than in the treated group but it should be remembered that the proved comparability of the

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CHAPTER XXIII

Discussion and conclusion

The controlled clinical trial of which a full account has been given in the previous chapters shows that correctly managed long term treatment with dicoumarol of patients *under 60 years old* has resulted in a statistically significant reduction both in the incidence of recurrent infarction and in the mortality *during the first 12 months* after an acute infarct

The presumption that this statistical significance does not depend on chance is supported by making a comparison of many other factors in the treated and control groups all of which are in favour of the treated group (1) The incidence of recurrent infarction and the mortality in patients over 60 years during the first 12 months are also considerably lower in the treated than in the control group but the difference is not statistically significant (2) Attacks of severe retrosternal pain in which the presence of a recurrent infarction was suspected but not verified were observed about half as frequently in the treated group as in the control group (3) The morbidity from cardiovascular disease judged by the frequency and duration of admissions to hospital during the observation period is considerably lower in the treated than in the control group (4) Severe heart failure develops less often in treated than in untreated patients (5) The electrocardiogram more often returns to normal after the recorded infarct in the treated than in the control group (6) The incidence of thrombosis in a coronary artery shown at autopsy is significantly lower in the treated than in the control group but it should be remembered that the proved comparability of the two groups probably does not hold good for the post mortem cases in each group

The greatest difference between treated and untreated cases and the only difference which is statistically significant with the level used (5 %) is thus in the incidence of recurrent infarction and the deaths in patients *under 60 years old* and *during the first 12 months* These two points will now be examined in more detail

Age factor It might at first seem surprising that the treatment had most effect in the younger age groups The number of observations (recurrent infarcts deaths) is certainly considerably larger among the oldest cases so that this group should numerically be the best for showing the effect of treatment All the same it is among the younger cases (under 60 years) that the difference is statistically significant

Previous studies of the prognosis have shown that the mortality ratio after myocardial infarction is considerably higher in relatively young than in older

patients This is shown especially clearly in *Westlund and Hougen's* investigation from Oslo (1956) (see also p 25) They found that the mortality ratio (ratio between actual and expected number of deaths) in the first year after discharge varied from 15 5 at ages 40–49 to 4 8 at ages 80–89 The mortality ratio which can be counteracted by treatment is thus considerably higher among the younger age groups

Although as far as the author is aware it has not been especially investigated or proved it is reasonable to assume that *thrombosis* is relatively more important in the aetiology of coronary occlusion and in the deaths from coronary disease in the younger than in the older age groups It is therefore not unreasonable after all that one achieves less with long term anticoagulant therapy in older patients who probably more often have advanced coronary *sclerosis* and a more damaged myocardium than younger patients

It should perhaps be pointed out here that the incidence of recurrent infarction and the mortality were high and there was no special difference between the treated and control groups in the group of patients in this investigation who had had more than one infarct before the beginning of the observation period Although this group of patients was small the results seem to indicate that the effect of treatment is slight or uncertain in patients with recurrent infarction It was also found that the effect of the treatment seems to be better in patients with normal cardiac volume than in those with an enlarged heart

Together with the demonstration of the definite effect in the younger age groups this finding is of considerable practical interest It is in contrast with previously predominant ideas of the indications for treatment which are usually based chiefly on theoretical considerations Thus in 1944 when *Nichol* introduced this treatment into cardiology it was for patients with a tendency to recurrent infarction *(Nichol and Fasset 1947)* Since then Nichol and his co workers have used this treatment in coronary disease with many different indications including cases of impending infarction (see p 36 and *Nichol* 1950) *Wright and co workers* (see pp 33–34) maintain that long term anticoagulant therapy is indicated in *recurrent* myocardial infarction especially if there are thromboembolic complications or if periods of heart failure are a predominant feature *Suzman Ruskin and Goldberg* (1954) are of a similar opinion on the basis of their investigation (see pp 37–38) Patients in whom the presenting attack is mild in addition to being the first one and who receive short term anticoagulant therapy show a favourable outlook in respect of subsequent infarction cardiac failure and death irrespective of whether or not the anticoagulant therapy is continued indefinitely By contrast the patients most likely to benefit from long term anticoagulant therapy are those in whom not only is the presenting attack severe but there is also a history of previous myocardial infarction

On the other hand *Waaler* (1956) has found after a thorough study of angina pectoris patients with long term therapy from Owren's material that there is a

statistically significantly lower mortality among patients in whom treatment is started within a year of diagnosis (See also p 35) *Olsen Kahrs Rømcke and Langjærde* (1956) have investigated the long term prognosis among untreated infarction patients who were divided in retrospect into good risks and poor risks They found that the patients in the good risk group more often died of new infarcts whereas patients in the poor risk group more often died of heart failure They maintain that there is thus a theoretical basis for giving long term anticoagulant therapy primarily to the good risks

Owren (1955) strongly emphasises that long term anticoagulant treatment is prophylactic and not curative The results of the present controlled investigation support this opinion in old patients and those with multiple previous infarcts where there must be assumed to be extensive and irreparable damage of the coronary circulation and of the myocardium the treatment seems to be of little value The most definite and greatest effect was in the younger patients who had only had one previous infarct Paradoxically it can perhaps be said that whereas short term treatment in acute myocardial infarction is primarily indicated in poor risks long term therapy is primarily indicated in good risks

Time factor In patients under 60 years old *a definite effect of treatment can only be demonstrated during the first 12 months* as mentioned previously Later on there is no obvious difference between the treated and control groups The limit of 12 months was chosen arbitrarily The figures seem to indicate that the difference was greatest in the first 6 months

Most of the earlier prognosis studies show that the first year after an acute infarct is more dangerous and the mortality ratio is higher than in subsequent periods This is especially well illustrated by *Westlund and Hougen* (1956) (see also page 25) They found that the mortality ratio (ratio between actual and expected number of deaths) among males 60–69 years old varied from 8 1 in the first year after discharge to 2 1 ten years and over It therefore seems reasonable that the treatment should achieve most in the first period in which the mortality ratio and also the incidence of new or extended coronary thrombosis and recurrent infarction are highest It is also primarily in this period that collateral vessels develop and possibly also recanalisation occurs which are so important for the prognosis

On the other hand it is also clear that even though in this study no difference was found between the treated and untreated cases after the first year the possibility has not been excluded that the treatment *could* have a definite effect for a longer period During the first year selection of the material took place as more of the worse cases died in the control than in the treated group A bias thus arose in disfavour of the treatment and this might have prevented recognition of the possible development of a real difference It is impossible to state how large a part this has played in this investigation In order to assess the effect of treatment definitely for instance in the period from 12–24 months after an acute infarct

patients should be investigated who had *all* been treated (or not treated) for the whole of the first 12 months Subsequently for example by drawing lots this material should be assigned to a treated and an untreated (or placebo treated) group which would then be observed for the following 12 months

In the author s opinion future controlled clinical trials of the effect of long term anticoagulant therapy should aim at assessing the effect over a limited period This would greatly simplify the problems and have many practical and statistical advantages

In this study the results were achieved after treatment with dicoumarol which was both consistent and intensive (see Chapter IX) The treatment was at any rate considerably more intensive than that in the few previous investigations in which such information is given In the author s opinion there is no reason to believe that one could achieve better results with this form of anticoagulant therapy This is confirmed by the fact that cases of recurrent infarction and sudden death in the treated group with very few exceptions occurred when the treatment was adequate and the PP values were low (see Chapter XII) They were therefore not caused by a relative reduction in the intensity of treatment

In spite of this intensive treatment haemorrhagic complications were not a serious problem (see Chapter XIII) The incidence of haemorrhages was no larger than that in the large investigations previously published by experts It is worthy of note that the incidence of severe cerebral vascular accidents was similar in the control group and in the treated group although as would be expected the mortality from this condition was higher in the treated group

This study has thus shown that long term treatment with dicoumarol after acute myocardial infarction has a definite effect but that this effect has marked limitations Treatment is far from providing absolute prophylaxis for recurrent infarction and sudden cardiac death This is not surprising seen in the light of the theoretical considerations in Chapter II and in the knowledge that thrombosis seems to be the cause of coronary occlusion and of death from coronary disease in only 50 % of cases In this investigation as a whole treatment during the observation period has resulted in a reduction in the incidence of recurrent infarction by about 45 % and in the mortality from cardiovascular diseases by about 37 % When it is remembered that treatment with dicoumarol has no absolute antithrombotic effect these results seem to be theoretically reasonable In this study thromboembolic complications other than coronary thrombosis seem to be very infrequent in myocardial infarction after the acute phase and they are therefore not an indication for long term treatment Exceptions to this appear to be only the cases in whom besides coronary disease there are signs of peripheral obliterating arteriosclerosis with the possibility of secondary thrombosis

The limited effect of the treatment is demonstrated most clearly by the fact previously mentioned that a statistically significant effect was only shown in

patients under 60 years old during the first 12 months of the observation period The age limit (60 years) and the limit of duration (12 months) have been chosen arbitrarily Thus as mentioned it has not been proved that long term dicoumarol therapy in older patients and for longer periods is ineffective There are in this investigation different observations which seem to indicate that the opposite may be true There is however a very clear *difference in the grade of effect* between younger and older patients and between the first 6–12 months and later periods This *quantitative difference* is of great practical significance when considering the indications for treatment

The effect of treatment shown in this investigation is in the opinion of the author not such that it justifies long term treatment throughout life of *all* patients with myocardial infarction with the enormous consequences this would have It would usually be both practically and economically impossible It seems on the contrary that the indications for this form of treatment should be different and stricter than those previously employed The results of the controlled clinical trial give reason to believe that the energy available in medical departments laboratories and among specialists would be most profitably expended on relatively young patients who have only had one infarct Thus far more would probably be achieved by treating all or a large number of these patients for for example 6 months or a year than by treating a smaller unselected number of infarction patients for the rest of their lives

General summary

The object of this study has been to investigate the prophylactic value of long term treatment with dicoumarol after acute myocardial infarction.

In *Chapter I* the background to the study is mentioned. A short account is given of the discovery of dicoumarol, its introduction into clinical medicine and the results of anticoagulant therapy in acute myocardial infarction.

In *Chapter II* the problem of the investigation is presented. This is followed by an account of the theoretical and practical considerations for the solution of the problem. On the basis of the literature the most important factors in the *pathogenesis of coronary occlusion* are discussed with special reference to the significance of thrombosis as the cause of the occlusion. Previous investigations indicate that thrombosis is only the cause of coronary occlusion in about 50 % of the cases. This gives a theoretical limitation of the prophylactic value of anticoagulant therapy. Details are also given of the possibility that thrombosis may be a contributory cause of atherosclerosis, as has been recently maintained by some investigators, especially Duguid.

Bearing in mind the question of whether or not the problem of the investigation can be solved within a reasonable time, an account is then given of previous experiences of the *prognosis after acute myocardial infarction*. The prognosis varies markedly in different publications. The reasons for this are discussed briefly. On the whole, however, the prognosis is bad enough for the possible effect of prophylactic therapy to be evident within a few years.

In the last section of this chapter it is shown that there were good opportunities for collecting a sufficiently large number of patients who would be able to be under continued supervision. Further, an account is given of the theoretical background for Owren's PP method of prothrombin and proconvertin estimation, which in this study is the basis for control of the antithrombotic effect during treatment.

In *Chapter III* a brief account is given of the previous publications on long term anticoagulant therapy. It is evident that the main aims of most previous publications have been to show, firstly, that treatment of ambulant patients is practicable and, secondly, how it should be carried out. Only a few articles have attempted to demonstrate the effect of treatment, and satisfactorily planned and controlled clinical trials have not been published. If the technique of control of dosage is satisfactory, haemorrhagic complications are not a very great problem

At any rate they give no reason for rejecting the treatment There is a great need for controlled investigations which are able to clarify the effect of and indications for treatment

In *Chapter IV* more details are given of the plans for the investigation especially the method chosen for allotting patients to treated and control groups It is shown that neither the investigator the doctor referring the case nor anyone else who might have a subjective point of view have influenced the assignment of patients to the groups The only exceptions to this were a few patients who had to be excluded because they could not attend out patient clinics The principles for this exclusion were uniform in the treated and control groups

Details are also given of the lines followed in the clinical investigation of the patients in hospital and of the precautions taken to ensure that all the patients had as similar investigations as possible Finally an account is given of some special investigation techniques especially the method for estimation of prothrombin and proconvertin Owren s P P method which plays an important part in this investigation

In *Chapter V* the material is discussed In all the raw material consisted of 277 consecutive patients They were all under 76 years old and had survived an acute myocardial infarct by a minimum of one month (30 days) and a maximum of two months Next the number of patients in each group is mentioned that had to be excluded from the investigation as on account of illness geographic conditions or for other reasons they were not able to attend the necessary out patient clinics for supervision and treatment A few additional patients had to be excluded as for reasons outside the influence of the investigator they did not satisfy the requirements for the clinical trial The original material consisting of 277 cases and termed section A was thus reduced to 237 cases (119 treated and 118 control) which formed the basis for the controlled clinical trial and was termed section B

In *Chapter VI* a detailed analysis and statistical comparison of the treated and control groups is given in order to show the comparability of the two groups at the beginning of the investigation This comparison was made both for section A and for section B This was done in order to find out whether the exclusion of patients had biased the comparability in any way The statistical comparison was made for many different criteria which fall into 3 main groups I General characteristics II Facts in the past history thought to have significance for the prognosis III Course of the recorded infarct

Apart from a couple of differences caused by errors in investigation technique there was no significant difference with the 5 % level of statistical significance between the treated and control groups either in section A or section B In all the statistical comparison of the treated and control groups provides *a good basis for stating that the patients were allotted by chance to the two groups*

In *Chapter VII* an account is given of the treatment in hospital during the

acute phase of the infarct The conditions governing the medical care nursing and general care were uniform for all the patients and in this respect there was no difference between the treated and control groups An analysis of the main cardiological treatment also showed very uniform conditions in the two groups

All the patients in both groups had anticoagulant treatment with dicoumarol during the first month and this treatment was supervised and the doses prescribed by the author in all cases There is therefore no evidence for any differences in the administration of dicoumarol Both thromboembolic and haemorrhagic complications occurred infrequently during the acute phase and their distribution was almost exactly the same in the treated and control groups There was no evidence that the treatment in hospital during the acute phase of the infarct had biased the comparability of the groups thus influencing the subsequent comparison

In *Chapter VIII* an account is given of the lines followed in the observation and treatment of patients in the ambulant phase All the patients in both groups had regular cardiological supervision by the author Great efforts were made to give the patients in the control group as thorough supervision and treatment apart from the use of dicoumarol as the patients in the treated group An account is given of the general lines followed for dosage and control of dicoumarol therapy Finally it is shown that the length of the observation period is completely comparable in the treated and control groups and that collection of the material has taken place over exactly the same period (3 years)

In *Chapter IX* an account is given of the intensity of the anticoagulant therapy as judged by the PP values recorded during the observation period Such information is of great significance and interest but is only given exceptionally in previous publications It was calculated that the PP value was under 30 % (i e 29 % or less) for 82 5 % of the period of treatment and under 40 % for 92 3 % of the period The value was in the range 10–19 % for about 46 % of the period The intensity of the treatment was also calculated in each individual patient It was shown that the PP value was under 30 % for 70–100 % of the period of treatment in 103 of the 119 patients In comparison with the information from other investigations this treatment must be considered to be very intensive and effective and it is reckoned that the antithrombotic effect of dicoumarol has been used to the full In the control group anticoagulant therapy was only given as short term treatment of recurrent infarction and of a few other thromboembolic episodes

In *Chapter X* recurrent infarction during the observation period in the treated and control groups is discussed Details are given of the method of diagnosis and of the criteria for the different grades of diagnostic certainty Next an account is given of the incidence of recurrent infarction in relation to sex and age A thorough statistical investigation is also made of the "force of recurrence i e the probability per unit of time at a given point of time in the observation period that recurrent infarction will occur This investigation shows that *with 5 % level*

the force of recurrence for patients under 60 years old is significantly higher in the control than in the treated group during the first 12 months of the observation period The difference in patients over 60 years has the same trend but is not statistically significant After 12 months there is no definite difference between the groups either over or under 60 There is evidence that the force of recurrence was especially high in patients who had had several previous infarcts and that treatment of such cases may have least prophylactic effect It has also been shown that the force of recurrence increases with increasing cardiac volume

In *Chapter VI* the mortality during the observation period is discussed An account is given of the information received about the deaths and the causes of death The relation of mortality to both age and sex is given Next a thorough statistical investigation is made of the force of mortality i e the probability per unit of time at a given point of time in the observation period that death will occur This showed that *with 5 % level the force of mortality in patients under 60 years is significantly higher in the control than in the treated group during the first 12 months of the observation period* The difference in patients of 60 years and over during the same period is not statistically significant After 12 months there is no certain difference between the groups either over or under 60 The investigation also shows that the mortality is relatively high in patients who have had several previous infarcts and it appears that treatment is not especially indicated in such cases as has previously been assumed The mortality also increases with increasing cardiac volume and anticoagulant therapy seems to have more effect in patients with a normal sized than in those with an enlarged heart

In *Chapter VII* a detailed account is given of the PP level both in the weeks preceeding and in direct relation to the 26 recurrent infarcts and 5 cases of sudden death that occurred in the treated group It is shown that a relative reduction of the intensity of the treatment cannot have played an important part in causing these episodes Most of them occurred while the PP level was under 30 %

In *Chapter VIII* an account is given of the number type and degree of severity of the haemorrhagic complications during treatment with dicoumarol In all one haemorrhagic episode was observed every 7 9 years of treatment per patient and one moderate or severe haemorrhage every 13 1 years of treatment per patient In spite of the intensity of the treatment the incidence of haemorrhage is no higher than that observed in previous large investigations by experts About half the haemorrhagic episodes occurred while the PP value was under 10 % and in the other half the PP value was between 10 and 34 % In a good 1/3 of the cases contributory local causes apart from anticoagulant therapy were found Four cases of cerebral haemorrhage occurred all of which were fatal However in the control group there were also 5 severe cerebral vascular accidents one of which was fatal and 3 of the others resulted in permanent invaliding hemiparesis Apart

from these cases there were only 4 cases of moderate haemorrhage during the observation period in the control group

In *Chapter VII* an account is given of the tests carried out to investigate the liver function during the long term treatment with dicoumarol With the tests used no sign of liver damage was demonstrated apart from 4 cases in which the thymol turbidity test became positive during the treatment period for unknown reasons

In *Chapter XI* details are given of the patients mode of life ability to work and morbidity during the observation period No important difference was shown between the groups with regard to mode of life ability to work and type of work However the incidence was higher and the duration of admissions to hospital longer for cardiovascular disease during the observation period for patients in the control than in the treated group There was however no difference between the groups in morbidity from intercurrent diseases Severe heart failure was observed in 3 times as many patients in the control group as in the treated group 12 and 4 cases respectively A detailed investigation was not made into the prophylactic effect of treatment against attacks of angina pectoris but a rough comparison was made for the two groups and showed no convincing difference The number of cases with increase in size of the heart (estimated radiologically) was also about equal in the two groups A lasting return to normal of the electrocardiogram after the recorded infarct was observed in 28 patients in the treated group and 17 in the control group Intermittent claudication developed during the observation period in 8 patients in the control group and only 1 in the treated group who had not previously had this symptom Other extra cardiac thromboembolic complications in the control group included only one case of thrombophebitis and one case of pulmonary embolism

In *Chapter XII* the medical and psychological significance of regular supervision of patients after myocardial infarction is discussed briefly and the need for such supervision is emphasised

In *Chapter XIII* details are given of the autopsies carried out in 43 of the 66 cases who died during the observation period The presence of the originally diagnosed acute infarct was verified in all the post mortem cases Both coronary thrombosis and other thromboembolic phenomena were shown at autopsy 2–3 times as frequently in the control as in the treated group The incidence of coronary thrombosis was significantly higher in the control than in the treated group but it should be remembered that the proved comparability of the two groups probably does not hold good for the post mortem cases in each group The results indicate that long term treatment with dicoumarol does have an anti thrombotic effect on the development of coronary thrombosis but at the same time it does not provide complete prophylaxis On the whole the autopsy finding support the previously mentioned investigations into the clinical effect The weight of the heart was increased in relation to the average standard values

in all the post mortem cases In most cases the increase in weight was considerable

In *Chapter XVIII* there is a brief discussion of the results of the controlled clinical trial Besides the statistically proved difference in the forces of recurrence and of mortality in patients under 60 years old and in the first 12 months the effect of treatment is substantiated by many other observations most of which have been mentioned earlier in this summary The influence of the age factor and the time factor on the effect of treatment is discussed in more detail It is emphasized that the effect is greatest in the first 6–12 months after the acute infarct It is further pointed out that the results of this investigation seem to be theoretically reasonable in the light of previous pathological observations and studies of the long term prognosis after acute myocardial infarction Although the view usually held previously has been that treatment is especially indicated in patients with recurrent infarction and the worse cases after severe infarction with a tendency to heart failure and thromboembolic episodes this investigation has shown that it is primarily the younger patients and those who have only had one infarct who benefit from this form of treatment This is reasonable when it is remembered that the treatment is primarily prophylactic and not curative Paradoxically it can therefore perhaps be said that while short term treatment of acute myocardial infarction is primarily indicated in the so called poor risk cases long term therapy is primarily indicated in the good risk cases

Appendix

During the preparation and printing of this study the patients in both groups have been under observation for another 11 months from Feb 1st 1956 to Jan 1st 1957 A brief survey of the incidence of recurrent infarction and the mortality during this period may be of interest

All the patients in the treated group have continued the treatment except for one case in which dicoumarol was stopped after serious haematemesis and melaena (see pp 165–166) The patients in the control group were as before only given short term anticoagulant treatment when recurrent infarction or other thromboembolic complications occurred

Reckoning from the beginning of the observation period in each individual case either till death or to Jan 1st 1957 it was found that the total sum of the observation times for the 119 patients in the treated group was 6041 months (503 4 years) and for the 118 patients in the control group it was 5128 months (427 3 years)

The observation time for the patients in both groups who were still alive on Jan 1st 1957 varied between 42 and 79 months In the treated group the average duration of observation for these patients was 58 3 months and in the control group it was 57.2 months

On Feb 1st 1956 there were 95 patients alive in the treated group and 76 in the control group The incidence of recurrent infarction and the mortality among these patients in the following 11 months are shown in *Tables 1 and 2*

TABLE 1

The incidence of recurrent infarction in the period from Feb 1st 1956 to Jan 1st 1957

Age group	Number of cases		Number of cases with recurrence	
	Treated	Control	Treated	Control
Under 60 years	53	44	3 (1)	3
60 years and over	42	32	4 (3)	2
Total	95	76	7 (4)	5

The ages given are the ages on admission for the first recorded acute infarct The figures in brackets refer to the number of deaths

TABLE 2

Number of deaths in the period from Feb 1st 1956 to Jan 1st 1957

Causes of death

Cause of death	Patients under 60 years Treated	Patients under 60 years Control	Patients 60 years and over Treated	Patients 60 years and over Control
Recurrent infarction	1	0	3	0
Sudden death	2	1	0	2
Heart failure	0	0	0	1
Heart failure and embolism	0	0	0	2
Total number of deaths	3	1	3	5

Except for two cases one in the treated and one in the control group in which the diagnosis was considered to be *very probable* all the cases shown in Table 1 were *definite* recurrent infarcts (see p 121)

The dicoumarol therapy was very stable and satisfactory in the weeks before the episodes of recurrent infarction and sudden death in all cases The PP values in direct relation to 6 of the 7 cases of recurrent infarction were 11 12 14 18 26 and 29 % respectively In the seventh case the PP value was 18 % three days before the patient died of a very probable recurrent infarct The PP values in the 2 cases of sudden death in the treated group had been estimated three and seven days before the episode and were 16 and 20 respectively

Post mortems were carried out in 6 of the 12 cases who died in the above mentioned period 3 in each group In the treated group a fresh recurrent infarct was found in all 3 cases In the control group post mortems were carried out in two cases who had been treated in the hospital for severe heart failure before death Besides finding signs of congestion in the visceral organs pulmonary embolism was verified as the cause of death in one of these cases In the other case embolism in the left femoral artery was diagnosed clinically and verified at autopsy In the last weeks before death this patient had had persistant atrial flutter In one case in the control group who died suddenly no signs of fresh infarction or coronary thrombosis were found at autopsy

It appears from Tables 1 and 2 that there is no obvious difference in the incidence of recurrent infarction and in the mortality between the treated and control group in the above mentioned period of observation These findings therefore support the findings previously discussed i e that the treatment is most effective in the first period after an acute infarct

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